

WE CLAIM:

1. A method of detecting a nucleic acid having at least two portions comprising:

providing a type of nanoparticles having oligonucleotides attached thereto, the  
5 oligonucleotides on each nanoparticle having a sequence complementary to the sequence of at least two portions of the nucleic acid;

contacting the nucleic acid and the nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the two or more portions of the nucleic acid; and

10 observing a detectable change brought about by hybridization of the oligonucleotides on the nanoparticles with the nucleic acid.

2. A method of detecting nucleic acid having at least two portions comprising:

15 contacting the nucleic acid with at least two types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on the first type of nanoparticles having a sequence complementary to a first portion of the sequence of the nucleic acid, the oligonucleotides on the second type of nanoparticles having a sequence complementary to a second portion of the sequence of the nucleic acid, the contacting  
20 taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the nucleic acid; and

observing a detectable change brought about by hybridization of the oligonucleotides on the nanoparticles with the nucleic acid.

25 3. The method of Claim 2 wherein the contacting conditions include freezing and thawing.

4. The method of Claim 2 wherein the contacting conditions include heating.



the nucleic acid.

12. The method of Claim 2 wherein the nucleic acid is viral RNA or DNA.

13. The method of Claim 2 wherein the nucleic acid is a gene associated with  
5 a disease.

14. The method of Claim 2 wherein the nucleic acid is a bacterial DNA.

15. The method of Claim 2 wherein the nucleic acid is a fungal DNA.  
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16. The method of Claim 2 wherein the nucleic acid is a synthetic DNA, a  
synthetic RNA, a structurally-modified natural or synthetic RNA, or a structurally-  
modified natural or synthetic DNA.

17. The method of Claim 2 wherein the nucleic acid is from a biological  
15 source.

18. The method of Claim 2 wherein the nucleic acid is a product of a  
polymerase chain reaction amplification.  
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19. The method of Claim 2 wherein the nucleic acid is contacted with the first  
and second types of nanoparticles simultaneously.

20. The method of Claim 2 wherein the nucleic acid is contacted and  
25 hybridized with the oligonucleotides on the first type of nanoparticles before being  
contacted with the second type of nanoparticles.

21. The method of Claim 20 wherein the first type of nanoparticles is attached

to a substrate.

22. The method of Claim 2 wherein the nucleic acid is double-stranded and hybridization with the oligonucleotides on the nanoparticles results in the production of a triple-stranded complex.

23. A method of detecting nucleic acid having at least two portions comprising:

providing a substrate having a first type of nanoparticles attached thereto, the nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid to be detected;

contacting said nucleic acid with the nanoparticles attached to the substrate under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with said nucleic acid;

providing a second type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to one or more other portions of the sequence of said nucleic acid;

contacting said nucleic acid bound to the substrate with the second type of nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the second type of nanoparticles with said nucleic acid; and

observing a detectable change.

24. The method of Claim 23 wherein the substrate has a plurality of types of nanoparticles attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

25. A method of detecting nucleic acid having at least two portions

comprising:

providing a substrate having a first type of nanoparticles attached thereto, the nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid to be  
5 detected;

contacting said nucleic acid with the nanoparticles attached to the substrate under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with said nucleic acid;

providing a second type of nanoparticles having oligonucleotides attached  
10 thereto, the oligonucleotides having a sequence complementary to one or more other portions of the sequence of said nucleic acid;

contacting said nucleic acid bound to the substrate with the second type of nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the second type of nanoparticles with said nucleic acid;

providing a binding oligonucleotide having a selected sequence having at  
15 least two portions, the first portion being complementary to at least a portion of the sequence of the oligonucleotides on the second type of nanoparticles;

contacting the binding oligonucleotide with the second type of nanoparticles bound to the substrate under conditions effective to allow hybridization of  
20 the binding oligonucleotide to the oligonucleotides on the nanoparticles;

providing a third type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to the sequence of a second portion of the binding oligonucleotide;

contacting the third type of nanoparticles with the binding oligonucleotide  
25 bound to the substrate under conditions effective to allow hybridization of the binding oligonucleotide to the oligonucleotides on the nanoparticles; and

observing a detectable change.

26. The method of Claim 25 wherein the substrate has a plurality of types of nanoparticles attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

5           27. A method of detecting nucleic acid having at least two portions comprising:

                    contacting a nucleic acid to be detected with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under  
10           conditions effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

                    contacting said nucleic acid bound to the substrate with a first type of nanoparticles having one or more types of oligonucleotides attached thereto, at least one of the types of oligonucleotides having a sequence complementary to a second portion of  
15           the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with said nucleic acid;

                    contacting the first type of nanoparticles bound to the substrate with a second type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on the second type of nanoparticles having a sequence complementary  
20           to at least a portion of the sequence of one of the types of oligonucleotides on the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles; and  
                    observing a detectable change.

25           28. The method of Claim 27 wherein the first type of nanoparticles has only one type of oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to the second portion of the sequence of said nucleic acid and to at least a portion of the sequence of the oligonucleotides on the second type of nanoparticles.

29. The method of Claim 28 further comprising contacting the second type of nanoparticles bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles.

30. The method of Claim 27 wherein the first type of nanoparticles has at least two types of oligonucleotides attached thereto, the first type of oligonucleotides having a sequence complementary to the second portion of the sequence of said nucleic acid, and the second type of oligonucleotides having a sequence complementary to the sequence of at least a portion of the oligonucleotides on the second type of nanoparticles.

31. The method of Claim 30 further comprising contacting the second type of nanoparticles bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles.

32. The method of Claim 27 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

33. The method of any one of Claims 23-32 wherein the substrate is a transparent substrate or an opaque white substrate.

34. The method of Claim 33 wherein the detectable change is the formation of dark areas on the substrate.

35. The method of any one of Claims 23-32 wherein the nanoparticles are

made of gold.

36. The method of any one of Claims 23-32 wherein the substrate is contacted with silver stain to produce the detectable change.

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37. The method of any one of Claims 23-32 wherein the detectable change is observed with an optical scanner.

38. A method of detecting nucleic acid having at least two portions comprising:

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contacting a nucleic acid to be detected with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

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contacting said nucleic acid bound to the substrate with a type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a second portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with said nucleic acid;

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contacting the substrate with silver stain to produce a detectable change;  
and

observing the detectable change.

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39. The method of Claim 38 wherein the nanoparticles are made of a noble metal.

40. The method of Claim 39 wherein the nanoparticles are made of gold or silver.



41. The method of Claim 38 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

5           42. The method of any one of Claims 38-41 wherein the detectable change is observed with an optical scanner.

43. A method of detecting nucleic acid having at least two portions comprising:

10           contacting a nucleic acid to be detected with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

15           contacting said nucleic acid bound to the substrate with liposomes having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the liposomes with said nucleic acid;

20           contacting the liposomes bound to the substrate with a first type of nanoparticles having at least a first type oligonucleotides attached thereto, the first type of oligonucleotides having a hydrophobic group attached to the end not attached to the nanoparticles, the contacting taking place under conditions effective to allow attachment of the oligonucleotides on the nanoparticles to the liposomes as a result of hydrophobic  
25 interactions; and

observing a detectable change.

44. A method of detecting nucleic acid having at least two portions



45. The method of Claim 43 or 44 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

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46. The method of Claim 43 or 44 wherein the nanoparticles are made of gold.

47. The method of Claim 43 or 44 wherein the substrate is contacted with silver stain to produce the detectable change.

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48. The method of any one of Claims 43 or 44 wherein the detectable change is observed with an optical scanner.

49. A method of detecting nucleic acid having at least two portions comprising:

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providing a substrate having a first type of nanoparticles attached thereto, the nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid to be detected;

contacting said nucleic acid with the nanoparticles attached to the substrate under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with said nucleic acid;

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providing an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence complementary to a second portion of the sequence of said nucleic acid;

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contacting said nucleic acid bound to the substrate with the aggregate probe under conditions effective to allow hybridization of the oligonucleotides on the aggregate probe with said nucleic acid; and

observing a detectable change.

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50. The method of Claim 49 wherein the substrate has a plurality of types of nanoparticles attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

10 51. A method of detecting nucleic acid having at least two portions comprising:

providing a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid to be detected;

15 providing an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence  
20 complementary to a second portion of the sequence of said nucleic acid;

contacting said nucleic acid, the substrate and the aggregate probe under conditions effective to allow hybridization of said nucleic acid with the oligonucleotides on the aggregate probe and with the oligonucleotides on the substrate; and

observing a detectable change.

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52. The method of Claim 51 wherein said nucleic acid is contacted with the substrate so that said nucleic acid hybridizes with the oligonucleotides on the substrate, and said nucleic acid bound to the substrate is then contacted with the aggregate probe so

that said nucleic acid hybridizes with the oligonucleotides on the aggregate probe.

53. The method of Claim 51 wherein said nucleic acid is contacted with the aggregate probe so that said nucleic acid hybridizes with the oligonucleotides on the aggregate probe, and said nucleic acid bound to the aggregate probe is then contacted with the substrate so that said nucleic acid hybridizes with the oligonucleotides on the substrate.

54. The method of Claim 51 wherein said nucleic acid is contacted simultaneously with the aggregate probe and the substrate.

55. The method of Claim 51 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

56. A method of detecting nucleic acid having at least two portions comprising:

providing a substrate having oligonucleotides attached thereto;

providing an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence complementary to a first portion of the sequence of a nucleic acid to be detected;

providing a type of nanoparticles having at least two types of oligonucleotides attached thereto, the first type of oligonucleotides having a sequence complementary to a second portion of the sequence of said nucleic acid, the second type of oligonucleotides having a sequence complementary to at least a portion of the

sequence of the oligonucleotides attached to the substrate;

contacting said nucleic acid, the aggregate probe, the nanoparticles and the substrate, the contacting taking place under conditions effective to allow hybridization of said nucleic acid with the oligonucleotides on the aggregate probe and on the nanoparticles and hybridization of the oligonucleotides on the nanoparticles with the oligonucleotides on the substrate; and

observing a detectable change.

57. The method of Claim 56 wherein said nucleic acid is contacted with the aggregate probe and the nanoparticles so that said nucleic acid hybridizes with the oligonucleotides on the aggregate probe and with the oligonucleotides on the nanoparticles, and said nucleic acid bound to the aggregate probe and nanoparticles is then contacted with the substrate so that the oligonucleotides on the nanoparticles hybridize with the oligonucleotides on the substrate.

58. The method of Claim 56 wherein said nucleic acid is contacted with the aggregate probe so that said nucleic acid hybridizes with the oligonucleotides on the aggregate probe, said nucleic acid bound to the aggregate probe is then contacted with the nanoparticles so that said nucleic acid hybridizes with the oligonucleotides on the nanoparticles, and said nucleic acid bound to the aggregate probe and nanoparticles is then contacted with the substrate so that the oligonucleotides on the nanoparticles hybridize with the oligonucleotides on the substrate.

59. The method of Claim 56 wherein said nucleic acid is contacted with the aggregate probe so that said nucleic acid hybridizes with the oligonucleotides on the aggregate probe, the nanoparticles are contacted with the substrate so that the oligonucleotides on the nanoparticles hybridize with the oligonucleotides on the substrate, and said nucleic acid bound to the aggregate probe is then contacted with the

nanoparticles bound to the substrate so that said nucleic acid hybridizes with the oligonucleotides on the nanoparticles.

5           60. The method of Claim 56 wherein the substrate has the oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

10           61. The method of any one of Claims 49-60 wherein the substrate is a transparent substrate or an opaque white substrate.

          62. The method of Claim 61 wherein the detectable change is the formation of dark areas on the substrate.

15           63. The method of any one of Claims 49-60 wherein the nanoparticles in the aggregate probe are made of gold.

          64. The method of any one of Claims 49-60 wherein the substrate is contacted with a silver stain to produce the detectable change.

20           65. The method of any one of Claims 49-60 wherein the detectable change is observed with an optical scanner.

          66. A method of detecting nucleic acid having at least two portions comprising:

25                 contacting a nucleic acid to be detected with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the substrate with

said nucleic acid;

contacting said nucleic acid bound to the substrate with liposomes having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the liposomes with said nucleic acid;

providing an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a hydrophobic group attached to the end not attached to the nanoparticles;

contacting the liposomes bound to the substrate with the aggregate probe under conditions effective to allow attachment of the oligonucleotides on the aggregate probe to the liposomes as a result of hydrophobic interactions; and observing a detectable change.

67. The method of Claim 66 wherein the nanoparticles in the aggregate probe are made of gold.

68. The method of Claim 66 wherein the substrate is contacted with a silver stain to produce the detectable change.

69. The method of Claim 66 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

70. A method of detecting nucleic acid having at least two portions



comprising:

providing a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid to be detected;

5 providing a core probe comprising at least two types of nanoparticles, each type of nanoparticles having oligonucleotides attached thereto which are complementary to the oligonucleotides on at least one of the other types of nanoparticles, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of the oligonucleotides attached to them;

10 providing a type of nanoparticles having two types of oligonucleotides attached thereto, the first type of oligonucleotides having a sequence complementary to a second portion of the sequence of said nucleic acid, the second type of oligonucleotides having a sequence complementary to a portion of the sequence of the oligonucleotides attached to at least one of the types of nanoparticles of the core probe;

15 contacting said nucleic acid, the nanoparticles, the substrate and the core probe under conditions effective to allow hybridization of said nucleic acid with the oligonucleotides on the nanoparticles and with the oligonucleotides on the substrate and to allow hybridization of the oligonucleotides on the nanoparticles with the oligonucleotides on the core probe; and

20 observing a detectable change.

71. The method of Claim 70 wherein said nucleic acid is contacted with the substrate so that said nucleic acid hybridizes with the oligonucleotides on the substrate, and said nucleic acid bound to the substrate is then contacted with the nanoparticles so  
25 that said nucleic acid hybridizes with the oligonucleotides on the nanoparticles, and the nanoparticles bound to said nucleic acid are contacted with the core probe so that the oligonucleotides on the core probe hybridize with the oligonucleotides on the nanoparticles.



74. The method of any one of Claims 70-73 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

75. The method of any one of Claims 70-73 wherein the substrate is a transparent substrate or an opaque white substrate.

76. The method of Claim 76 wherein the detectable change is the formation of dark areas on the substrate.

77. The method of any one of Claims 70-73 wherein the nanoparticles in the core probe are made of gold.

78. The method of any one of Claims 70-73 wherein the substrate is contacted with a silver stain to produce the detectable change.

79. The method of any one of Claims 70-73 wherein the detectable change is observed with an optical scanner.

80. A method of detecting a nucleic acid having at least two portions comprising:

- providing nanoparticles having oligonucleotides attached thereto;
- providing one or more types of binding oligonucleotides, each of the binding oligonucleotides having two portions, the sequence of one portion being complementary to the sequence of one of the portions of the nucleic acid and the sequence of the other portion being complementary to the sequence of the



83. A method of detecting nucleic acid having at least two portions comprising:

contacting the nucleic acid with at least two types of particles having oligonucleotides attached thereto,

5 the oligonucleotides on the first type of particles having a sequence complementary to a first portion of the sequence of the nucleic acid and being labeled with an energy donor,

10 the oligonucleotides on the second type of particles having a sequence complementary to a second portion of the sequence of the nucleic acid and being labeled with an energy acceptor,

the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the particles with the nucleic acid; and

15 observing a detectable change brought about by hybridization of the oligonucleotides on the particles with the nucleic acid.

84. The method of Claim 83 wherein the energy donor and acceptor are fluorescent molecules.

20 85. A method of detecting nucleic acid having at least two portions comprising:

providing a type of microspheres having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of the nucleic acid and being labeled with a fluorescent molecule;

25 providing a type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a second portion of the sequence of the nucleic acid, nanoparticles being capable of producing a detectable change;

contacting the nucleic acid with the microspheres and the nanoparticles

under conditions effective to allow hybridization of the oligonucleotides on the microspheres and on the nanoparticles with the nucleic acid; and

observing a change in fluorescence, another detectable change produced by the nanoparticles, or both.

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86. The method of Claim 85 wherein the detectable change produced by the nanoparticles is a change in color.

10 87. The method of Claim 85 wherein the microspheres are latex microspheres and the nanoparticles are gold nanoparticles, and changes in fluorescence, color or both are observed.

15 88. The method of Claim 87 further comprising placing a portion of the mixture of the latex microspheres, nanoparticles and nucleic acid in an observation area located on a microporous material, treating the microporous material so as to remove any unbound gold nanoparticles from the observation area, and then observing the changes in fluorescence, color, or both.

20 89. A method of detecting nucleic acid having at least two portions comprising:

providing a first type of metallic or semiconductor nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of the nucleic acid and being labeled with a fluorescent molecule;

25 providing a second type of metallic or semiconductor nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a second portion of the sequence of the nucleic acid and being labeled with a fluorescent molecule;







the second container holding nanoparticles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a second portion of the nucleic acid.

5           100. The kit of Claim 99 comprising a third container holding oligonucleotides having a sequence complementary to a third portion of the nucleic acid, the third portion being located between the first and second portions.

10           101. The kit of Claim 99 wherein the nanoparticles are made of gold.

102. The kit of Claim 99 further comprising a solid surface.

15           103. A kit comprising at least two containers,  
the first container holding nanoparticles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a binding oligonucleotide, and

the second container holding one or more types of binding oligonucleotides, each of which has a sequence comprising at least two portions, the first portion being complementary to the sequence of the oligonucleotides on the nanoparticles  
20 and the second portion being complementary to the sequence of a portion of a nucleic acid.

25           104. The kit of Claim 103 which comprises additional containers, each holding an additional binding oligonucleotide, each additional binding oligonucleotide having a sequence comprising at least two portions, the first portion being complementary to the sequence of the oligonucleotides on the nanoparticles and the second portion being complementary to the sequence of another portion of the nucleic acid.

105. The kit of Claim 103 wherein the nanoparticles are made of gold.

106. The kit of Claim 103 further comprising a solid surface.

5 107. A kit comprising:

a container holding one type of nanoparticles having oligonucleotides attached thereto and one or more types of binding oligonucleotides, each of the types of binding oligonucleotides having a sequence comprising at least two portions, the first portion being complementary to the sequence of the oligonucleotides on the nanoparticles, whereby the binding oligonucleotides are hybridized to the oligonucleotides on the nanoparticles, and the second portion being complementary to the sequence of one or more portions of a nucleic acid.

108. A kit comprising at least one container, the container holding metallic or semiconductor nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a portion of a nucleic acid and having fluorescent molecules attached to the ends of the oligonucleotides not attached to the nanoparticles.

20 109. A kit comprising:

a substrate, the substrate having attached thereto nanoparticles, the nanoparticles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid; and

a first container holding nanoparticles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a second portion of the nucleic acid.

110. The kit of Claim 109 further comprising:

a second container holding a binding oligonucleotide having a selected sequence having at least two portions, the first portion being complementary to at least a portion of the sequence of the oligonucleotides on the nanoparticles in the first container; and

5           a third container holding nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to the sequence of a second portion of the binding oligonucleotide.

10           111. A kit comprising at least three containers:  
the first container holding nanoparticles;  
the second container holding a first oligonucleotide having a sequence complementary to the sequence of a first portion of a nucleic acid; and  
the third container holding a second oligonucleotide having a sequence complementary to the sequence of a second portion of the nucleic acid.

15           112. The kit of Claim 111 further comprising a fourth container holding a third oligonucleotide having a sequence complementary to the sequence of a third portion of the nucleic acid, the third portion being located between the first and second portions.

20           113. The kit of Claim 111 further comprising a substrate.

          114. The kit of Claim 113 further comprising:  
a fourth container holding a binding oligonucleotide having a selected sequence having at least two portions, the first portion being complementary to at least a  
25   portion of the sequence of the second oligonucleotide; and  
a fifth container holding an oligonucleotide having a sequence complementary to the sequence of a second portion of the binding oligonucleotide.

115. The kit of Claim 111 wherein the oligonucleotides, nanoparticles, or both bear functional groups for attachment of the oligonucleotides to the nanoparticles.

116. The kit of Claim 113 wherein the substrate, nanoparticles, or both bear functional groups for attachment of the nanoparticles to the substrate.

117. The kit of Claim 113 wherein the substrate has nanoparticles attached to it.

118. The kit of Claim 111 wherein the nanoparticles are made of gold.

119. A kit comprising:

a substrate having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid;

a first container holding nanoparticles having oligonucleotides attached thereto, some of which have a sequence complementary to the sequence of a second portion of the nucleic acid; and

a second container holding nanoparticles having oligonucleotides attached thereto which have a sequence complementary to at least a portion of the sequence of the oligonucleotides attached to the nanoparticles in the first container.

120. A kit comprising:

a substrate;

a first container holding nanoparticles;

a second container holding a first oligonucleotide having a sequence complementary to the sequence of a first portion of a nucleic acid;

a third container holding a second oligonucleotide having a sequence complementary to the sequence of a second portion of the nucleic acid; and

a fourth container holding a third oligonucleotide having a sequence

complementary to at least a portion of the sequence of the second oligonucleotide.

121. The kit of Claim 120 wherein the oligonucleotides, nanoparticles,  
substrate or all bear functional groups for attachment of the oligonucleotides to the  
5 nanoparticles or for attachment of the oligonucleotides to the substrate.

122. The kit of Claim 120 wherein the nanoparticles are made of gold.

123. A kit comprising:  
10 a substrate having oligonucleotides attached thereto which have a  
sequence complementary to the sequence of a first portion of a nucleic acid;  
a first container holding liposomes having oligonucleotides attached  
thereto which have a sequence complementary to the sequence of a second portion of the  
nucleic acid; and  
15 a second container holding nanoparticles having at least a first type of  
oligonucleotides attached thereto, the first type of oligonucleotides having a hydrophobic  
group attached to the end not attached to the nanoparticles.

124. The kit of Claim 123 wherein:  
20 the nanoparticles in the second container have a second type of  
oligonucleotides attached thereto, the second type of oligonucleotides having a sequence  
complementary to the sequence of the oligonucleotides on a second type of nanoparticles;  
and the kit further comprises:  
a third container holding a second type of nanoparticles having  
25 oligonucleotides attached thereto, the oligonucleotides having a sequence complementary  
to at least a portion of the sequence of the second type of oligonucleotides on the first  
type of nanoparticles.

125. A kit comprising:

a substrate, the substrate having attached thereto nanoparticles, the nanoparticles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid; and

5 a first container holding an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence  
10 complementary to a second portion of the sequence of the nucleic acid.

126. A kit comprising:

a substrate, the substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to the sequence of a first portion of a  
15 nucleic acid; and

a first container holding an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the  
20 aggregate probe having oligonucleotides attached thereto which have a sequence complementary to a second portion of the sequence of the nucleic acid.

127. The kit of Claim 126 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions  
25 of a single nucleic acid, the detection of multiple different nucleic acids, or both.

128. A kit comprising:

a substrate having oligonucleotides attached thereto;

a first container holding an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence complementary to a first portion of the sequence of the nucleic acid; and

a second container holding nanoparticles having at least two types of oligonucleotides attached thereto, the first type of oligonucleotides having a sequence complementary to a second portion of the sequence of the nucleic acid, and the second type of oligonucleotides having a sequence complementary to at least a portion of the sequence of the oligonucleotides attached to the substrate.

129. A kit comprising:

a substrate, the substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to the sequence of a first portion of a nucleic acid;

a first container holding liposomes having oligonucleotides attached thereto which have a sequence complementary to the sequence of a second portion of the nucleic acid; and

a second container holding an aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a hydrophobic group attached to the end not attached to the nanoparticles.

130. The kit of any one of Claims 125-129 wherein the substrate is a transparent substrate or an opaque white substrate.

131. The kit of any one of Claims 125-129 wherein the nanoparticles of the aggregate probe are made of gold.

5           132. A kit comprising at least three containers:  
              the first container holding nanoparticles;  
              the second container holding a first oligonucleotide having a sequence  
complementary to the sequence of a first portion of a nucleic acid; and  
              the third container holding a second oligonucleotide having a sequence  
10 complementary to the sequence of a second portion of the nucleic acid.

              133. The kit of Claim 132 further comprising a fourth container holding a third  
oligonucleotide having a sequence complementary to the sequence of a third portion of  
the nucleic acid, the third portion being located between the first and second portions.

15           134. The kit of Claim 132 further comprising a substrate.

              135. The kit of Claim 134 further comprising:  
              a fourth container holding a binding oligonucleotide having a selected  
20 sequence having at least two portions, the first portion being complementary to at least a  
portion of the sequence of the second oligonucleotide; and  
              a fifth container holding an oligonucleotide having a sequence  
complementary to the sequence of a second portion of the binding oligonucleotide.

25           136. The kit of Claim 132 wherein the oligonucleotides, nanoparticles, or both  
bear functional groups for attachment of the oligonucleotides to the nanoparticles.

              137. The kit of Claim 134 wherein the substrate, nanoparticles, or both bear



functional groups for attachment of the nanoparticles to the substrate.

138. The kit of Claim 134 wherein the substrate has nanoparticles attached to it.

5 139. The kit of Claim 132 wherein the nanoparticles are made of gold.

140. A kit comprising:

a substrate having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid;

10 a first container holding nanoparticles having oligonucleotides attached thereto, some of which have a sequence complementary to the sequence of a second portion of the nucleic acid; and

a second container holding nanoparticles having oligonucleotides attached thereto which have a sequence complementary to at least a portion of the sequence of the  
15 oligonucleotides attached to the nanoparticles in the first container.

141. A kit comprising:

a substrate;

a first container holding nanoparticles;

20 a second container holding a first oligonucleotide having a sequence complementary to the sequence of a first portion of a nucleic acid;

a third container holding a second oligonucleotide having a sequence complementary to the sequence of a second portion of the nucleic acid; and

25 a fourth container holding a third oligonucleotide having a sequence complementary to at least a portion of the sequence of the second oligonucleotide.

142. The kit of Claim 141 wherein the oligonucleotides, nanoparticles, substrate or all bear functional groups for attachment of the oligonucleotides to the

nanoparticles or for attachment of the oligonucleotides to the substrate.

143. The kit of Claim 141 wherein the nanoparticles are made of gold.

5 144. A kit comprising:

a substrate having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid;

10 a first container holding liposomes having oligonucleotides attached thereto which have a sequence complementary to the sequence of a second portion of the nucleic acid; and

a second container holding nanoparticles having at least a first type of oligonucleotides attached thereto, the first type of oligonucleotides having a hydrophobic group attached to the end not attached to the nanoparticles.

15 145. The kit of Claim 144 wherein:

the nanoparticles in the second container have a second type of oligonucleotides attached thereto, the second type of oligonucleotides having a sequence complementary to the sequence of the oligonucleotides on a second type of nanoparticles;

and the kit further comprises:

20 a third container holding a second type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to at least a portion of the sequence of the second type of oligonucleotides on the first type of nanoparticles.

25 146. A kit comprising at least two containers,

the first container holding particles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid, the oligonucleotides being labeled with an energy donor on the ends not

attached to the particles,

the second container holding particles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a second portion of a nucleic acid, the oligonucleotides being labeled with an energy acceptor on the ends not attached to the particles.

147. The kit of Claim 146 wherein the energy donor and acceptor are fluorescent molecules.

148. A kit comprising at least one container, the container holding a first type of particles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid, the oligonucleotides being labeled with an energy donor on the ends not attached to the particles, and a second type of particles having oligonucleotides attached thereto which have a sequence complementary to the sequence of a second portion of a nucleic acid, the oligonucleotides being labeled with an energy acceptor on the ends not attached to the particles.

149. The kit of Claim 148 wherein the energy donor and acceptor are fluorescent molecules.

150. A kit comprising:

a first container holding a type of microspheres having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid and being labeled with a fluorescent molecule; and

a second container holding a type of nanoparticles having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a second portion of the sequence of the nucleic acid.



156. A kit comprising a container holding an aggregate probe, the aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence complementary to a portion of the sequence of a nucleic acid.

157. A kit comprising a container holding an aggregate probe, the aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a hydrophobic group attached to the end not attached to the nanoparticles.

158. An aggregate probe, the aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a sequence complementary to a portion of the sequence of a nucleic acid.

159. The aggregate probe of Claim 158 comprising two types of nanoparticles each having two types of oligonucleotides attached thereto, the first type of oligonucleotides attached to each type of nanoparticles having a sequence complementary to a portion of the sequence of a nucleic acid, the second type of oligonucleotides attached to the first type of nanoparticles having a sequence complementary to at least a portion of the sequence of the second type of oligonucleotides attached to the second type

of nanoparticles.

160. The aggregate probe of Claim 158 comprising three types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides attached to the first type of nanoparticles having a sequence complementary to at least a portion of the sequence of the oligonucleotides attached to the second type of nanoparticles, the oligonucleotides attached to the second type of nanoparticles having a sequence complementary to at least a portion of the sequence of the oligonucleotides attached to the first type of nanoparticles, and the third type of nanoparticles having two types of oligonucleotides attached thereto, the first type of oligonucleotides having a sequence complementary to a portion of the sequence of a nucleic acid, and the second type of oligonucleotides having a sequence complementary to at least a portion of the sequence of the oligonucleotides attached to the first or second type of nanoparticles.

161. An aggregate probe, the aggregate probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe having oligonucleotides attached thereto which have a hydrophobic group attached to the end not attached to the nanoparticles.

162. A kit comprising a container holding a core probe, the core probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the core probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them.

163. The kit of Claim 162 further comprising a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion

of the sequence of a nucleic acid to be detected.

164. The kit of Claim 162 or 163 further comprising a container holding a type of nanoparticles having two types of oligonucleotides attached thereto, the first type of oligonucleotides having a sequence complementary to a second portion of the nucleic acid, and the second type of oligonucleotides having sequence complementary to a portion of the sequence of the oligonucleotides attached to at least one of the types of nanoparticles of the core probe.

165. The kit of Claim 162 or 163 further comprising a container holding a type of linking oligonucleotides comprising a sequence complementary to a second portion of the sequence of the nucleic acid and a sequence complementary to a portion of the sequence of the oligonucleotides attached to at least one of the types of nanoparticles of the core probe.

166. A core probe comprising at least two types of nanoparticles having oligonucleotides attached thereto, the nanoparticles of the core probe being bound to each other as a result of the hybridization of some of the oligonucleotides attached to them.

167. A substrate having nanoparticles attached thereto.

168. The substrate of Claim 167 wherein the nanoparticles have oligonucleotides attached thereto which have a sequence complementary to the sequence of a first portion of a nucleic acid.

169. A metallic or semiconductor nanoparticle having oligonucleotides attached thereto, the oligonucleotides being labeled with fluorescent molecules at the ends not attached to the nanoparticle.

170. A satellite probe comprising:

a particle having attached thereto oligonucleotides, the oligonucleotides having a first portion and a second portion, both portions having sequences complementary to portions of the sequence of a nucleic acid; and

probe oligonucleotides hybridized to the oligonucleotides attached to the nanoparticles, the probe oligonucleotides having a first portion and a second portion, the first portion having a sequence complementary to the sequence of the first portion of the oligonucleotides attached to the particles, both portions having sequences complementary to portions of the sequence of the nucleic acid, the probe oligonucleotides further having a reporter molecule attached to one end.

171. A method of nanofabrication comprising

providing at least one type of linking oligonucleotide having a selected sequence, the sequence of each type of linking oligonucleotide having at least two portions;

providing one or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each of the types of nanoparticles having a sequence complementary to the sequence of a portion of a linking oligonucleotide; and

contacting the linking oligonucleotides and nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles to the linking oligonucleotides so that a desired nanomaterial or nanostructure is formed wherein the nanoparticles are held together by oligonucleotide connectors.

172. The method of Claim 171 wherein at least two types of nanoparticles having oligonucleotides attached thereto are provided, the oligonucleotides on the first type of nanoparticles having a sequence complementary to a first portion of the sequence of a linking oligonucleotide, and the oligonucleotides on the second type of nanoparticles



having a sequence complementary to a second portion of the sequence of the linking oligonucleotide.

173. The method of Claim 171 or 172 wherein the nanoparticles are metallic  
5 nanoparticles, semiconductor nanoparticles, or a combination thereof.

174. The method of Claim 173 wherein the metallic nanoparticles are made of gold, and the semiconductor nanoparticles are made of CdSe/ZnS (core/shell).

10 175. A method of nanofabrication comprising:  
providing at least two types of nanoparticles having oligonucleotides attached thereto,  
the oligonucleotides on the first type of nanoparticles having a sequence complementary to that of the oligonucleotides on the second of the nanoparticles;  
15 the oligonucleotides on the second type of nanoparticles having a sequence complementary to that of the oligonucleotides on the first type of nanoparticles;  
and  
contacting the first and second types of nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles to each other  
20 so that a desired nanomaterial or nanostructure is formed.

176. The method of Claim 175 wherein the nanoparticles are metallic nanoparticles, semiconductor nanoparticles, or a combination thereof.

25 177. The method of Claim 176 wherein the metallic nanoparticles are made of gold, and the semiconductor nanoparticles are made of CdSe/ZnS (core/shell).

178. Nanomaterials or nanostructures composed of nanoparticles having

oligonucleotides attached thereto, the nanoparticles being held together by oligonucleotide connectors.

179. The nanomaterials or nanostructures of Claim 178 wherein at least some of  
5 the oligonucleotide connectors are triple-stranded.

180. The nanomaterials or nanostructures of Claim 178 wherein the  
nanoparticles are metallic nanoparticles, semiconductor nanoparticles, or a combination  
thereof.  
10

181. The nanomaterials or nanostructures of Claim 180 wherein the metallic  
nanoparticles are made of gold, and the semiconductor nanoparticles are made of  
CdSe/ZnS (core/shell).

182. A composition comprising at least two types of nanoparticles having  
oligonucleotides attached thereto, the oligonucleotides on the first type of nanoparticles  
having a sequence complementary to the sequence of a first portion of a nucleic acid or a  
linking oligonucleotide, the oligonucleotides on the second type of nanoparticles having a  
sequence complementary to the sequence of a second portion of the nucleic acid or  
20 linking oligonucleotide.

183. The composition of Claim 182 wherein the nanoparticles are metallic  
nanoparticles, semiconductor nanoparticles, or a combination thereof.

184. The composition of Claim 183 wherein the metallic nanoparticles are  
made of gold, and the semiconductor nanoparticles are made of CdSe/ZnS (core/shell).

185. An assembly of containers comprising:

a first container holding nanoparticles having oligonucleotides attached thereto, and

a second container holding nanoparticles having oligonucleotides attached thereto,

5 the oligonucleotides attached to the nanoparticles in the first container having a sequence complementary to that of the oligonucleotides attached to the nanoparticles in the second container,

the oligonucleotides attached to the nanoparticles in the second container having a sequence complementary to that of the oligonucleotides attached to the  
10 nanoparticles in the second container.

186. The assembly of Claim 185 wherein the nanoparticles are metallic nanoparticles, semiconductor nanoparticles, or a combination thereof.

15 187. The assembly of Claim 186 wherein the metallic nanoparticles are made of gold, and the semiconductor nanoparticles are made of CdSe/ZnS (core/shell).

188. A nanoparticle having a plurality of different oligonucleotides attached thereto.

20

189. A method of separating a selected nucleic acid having at least two portions from other nucleic acids, the method comprising:

providing two or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each of the types of nanoparticles having a  
25 sequence complementary to the sequence of one of the portions of the selected nucleic acid; and

contacting the nucleic acids and nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the selected

nucleic acid so that the nanoparticles hybridized to the selected nucleic acid aggregate and precipitate.

190. A method of binding oligonucleotides to charged nanoparticles to produce  
5 stable nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides having covalently bound thereto a moiety  
comprising a functional group which can bind to the nanoparticles;

10 contacting the oligonucleotides and the nanoparticles in water for a period  
of time sufficient to allow at least some of the oligonucleotides to bind to the  
nanoparticles;

adding at least one salt to the water to form a salt solution, the ionic  
strength of the salt solution being sufficient to overcome at least partially the electrostatic  
attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic  
repulsion of the oligonucleotides for each other; and

15 contacting the oligonucleotides and nanoparticles in the salt solution for an  
additional period of time sufficient to allow sufficient additional oligonucleotides to bind  
to the nanoparticles to produce the stable nanoparticle-oligonucleotide conjugates.

20 191. The method of Claim 190 wherein the nanoparticles are metal  
nanoparticles or semiconductor nanoparticles.

192. The method of Claim 191 wherein the nanoparticles are gold  
nanoparticles.

25 193. The method of Claim 192 wherein the moiety comprising a functional  
group which can bind to the nanoparticles is an alkanethiol.

194. The method of Claim 190 wherein all of the salt is added to the water in a

single addition.

195. The method of Claim 190 wherein the salt is added gradually over time.

5           196. The method of Claim 190 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium, chloride, sodium, acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

10           197. The method of Claim 196 wherein the salt is sodium chloride in a phosphate buffer.

15           198. The method of Claim 190 wherein nanoparticle-oligonucleotide conjugates are produced which have the oligonucleotides present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>.

20           199. The method of Claim 198 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.

25           200. The method of Claim 199 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm<sup>2</sup> to about 40 picomoles/cm<sup>2</sup>.

30           201. A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

            providing oligonucleotides, the oligonucleotides comprising at least one type of recognition oligonucleotides, each of the recognition oligonucleotides comprising

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a spacer portion and a recognition portion, the spacer portion being designed so that it can bind to the nanoparticles; and

contacting the oligonucleotides and the nanoparticles under conditions effective to allow at least some of the recognition oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

202. The method of Claim 201 wherein each of the spacer portions of the recognition oligonucleotides has a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

203. The method of Claim 201 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

204. The method of Claim 203 wherein the nanoparticles are gold nanoparticles.

205. The method of Claim 204 wherein the spacer portion comprises at least about 10 nucleotides.

206. The method of Claim 205 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

207. The method of Claim 206 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils, or all guanines.

208. A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

contacting the oligonucleotides with the nanoparticles under conditions effective to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

209. The method of Claim 208 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

210. The method of Claim 209 wherein the nanoparticles are gold nanoparticles.

211. The method of Claim 208 wherein each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion being designed so that it can bind to the nanoparticles.

212. The method of Claim 211 wherein each of the spacer portions of the recognition oligonucleotides has a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

213. The method of Claim 211 wherein the spacer portions of the recognition oligonucleotides comprises at least about 10 nucleotides.

214. The method of Claim 213 wherein the spacer portions of the recognition oligonucleotides comprises from about 10 nucleotides to about 30 nucleotides.

215. The method of Claim 211 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils or all guanines.

216. The method of Claim 211 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

5

217. The method of Claim 216 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

10

218. The method of Claim 208 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

219. A method of binding oligonucleotides to charged nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

15

providing oligonucleotides having covalently bound thereto a moiety comprising a functional group which can bind to the nanoparticles, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

20

contacting the oligonucleotides with the nanoparticles in water for a period of time sufficient to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles;

adding at least one salt to the water to form a salt solution, the ionic strength of the salt solution being sufficient to overcome at least partially the electrostatic attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic repulsion of the oligonucleotides for each other; and

25

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow additional oligonucleotides of each of the



types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

220. The method of Claim 219 wherein the nanoparticles are metal  
5 nanoparticles or semiconductor nanoparticles.

221. The method of Claim 220 wherein the nanoparticles are gold nanoparticles.

10 222. The method of Claim 221 wherein the moiety comprising a functional group which can bind to the nanoparticles is an alkanethiol.

223. The method of Claim 219 wherein all of the salt is added to the water in a single addition.  
15

224. The method of Claim 219 wherein the salt is added gradually over time.

225. The method of Claim 219 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium, chloride, sodium, acetate, ammonium acetate, a combination of two or more of these  
20 salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

226. The method of Claim 225 wherein the salt is sodium chloride in a  
25 phosphate buffer.

227. The method of Claim 219 wherein nanoparticle-oligonucleotide conjugates are produced which have the oligonucleotides are present on surface of the

nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>.

228. The method of Claim 227 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.

5

229. The method of Claim 228 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm<sup>2</sup> to about 40 picomoles/cm<sup>2</sup>.

10 230. The method of Claim 219 wherein each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion having attached to it the moiety comprising a functional group which can bind to the nanoparticles.

15 231. The method of Claim 230 wherein the spacer portion comprises at least about 10 nucleotides.

232. The method of Claim 231 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

20

233. The method of Claim 230 wherein the bases of the nucleotides of the spacers are all adenines, all thymines, all cytosines, all uracils, or all guanines.

25 234. The method of Claim 230 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

235. The method of Claim 234 wherein the sequence of the diluent

oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

236. The method of Claim 219 wherein the oligonucleotides comprise at least  
5 two types of recognition oligonucleotides.

237. Nanoparticle-oligonucleotide conjugates which are nanoparticles having  
oligonucleotides attached to them, the oligonucleotides being present on surface of the  
nanoparticles at a surface density sufficient so that the conjugates are stable, at least some  
10 of the oligonucleotides having a sequence complementary to at least one portion of the  
sequence of a nucleic acid or another oligonucleotide..

238. The conjugates of Claim 237 wherein the oligonucleotides are present on  
surface of the nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>  
15

239. The nanoparticles of Claim 238 wherein the oligonucleotides are present  
on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.

240. The nanoparticles of Claim 239 wherein the oligonucleotides are present  
20 on surface of the nanoparticles at a surface density of from about 15 picomoles/cm<sup>2</sup> to  
about 40 picomoles/cm<sup>2</sup>.

241. The nanoparticles of Claim 237 wherein the nanoparticles are metal  
nanoparticles or semiconductor nanoparticles.  
25

242. The nanoparticles of Claim 241 wherein the nanoparticles are gold  
nanoparticles.



about 40 picomoles/cm<sup>2</sup>.

251. The nanoparticles of Claim 243 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

5

252. The method of Claim 251 wherein the nanoparticles are gold nanoparticles.

10 253. Nanoparticles having oligonucleotides attached to them, the oligonucleotides comprising:

at least one type of recognition oligonucleotides, each of the types of recognition oligonucleotides comprising a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide; and

15 a type of diluent oligonucleotides.

15

254. The nanoparticles of Claim 253 wherein, each of the recognition oligonucleotides comprises a spacer portion and a recognition portion, the spacer portion being designed so that it is bound to the nanoparticles, the recognition portion having a sequence complementary to at least one portion of the sequence of a nucleic acid or  
20 another oligonucleotide.

20

255. The nanoparticles of Claim 254 wherein the spacer portion has a moiety covalently bound to it, the moiety comprising a functional group through which the spacer portion is bound to the nanoparticles.

25

256. The nanoparticles of Claim 254 wherein the spacer portion comprises at least about 10 nucleotides.

257. The nanoparticles of Claim 256 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

258. The nanoparticles of Claim 254 wherein the bases of the nucleotides of the spacer portion are all adenines, all thymines, all cytosines, all uracils or all guanines.

259. The nanoparticles of Claim 253 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>.

260. The nanoparticles of Claim 259 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.

261. The nanoparticles of Claim 260 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of from about 15 picomoles/cm<sup>2</sup> to about 40 picomoles/cm<sup>2</sup>.

262. The nanoparticles of Claim 254 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

263. The nanoparticles of Claim 262 wherein the sequence of the diluent oligonucleotides is the same as that of the spacer portions of the recognition oligonucleotides.

264. The nanoparticles of Claim 253 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

265. The nanoparticles of Claim 264 wherein the nanoparticles are gold nanoparticles.



comprising:

contacting the nucleic acid with at least two types of nanoparticle-oligonucleotide conjugates according to any one of Claims 237-240, the oligonucleotides on the nanoparticles of the first type of conjugates having a sequence complementary to a first portion of the sequence of the nucleic acid, the oligonucleotides on the nanoparticles of the second type of conjugates having a sequence complementary to a second portion of the sequence of the nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with the nucleic acid; and

observing a detectable change brought about by hybridization of the oligonucleotides on the nanoparticles with the nucleic acid.

270. The method of Claim 269 wherein the contacting conditions include freezing and thawing.

271. The method of Claim 269 wherein the contacting conditions include heating.

272. The method of Claim 269 wherein the detectable change is observed on a solid surface.

273. The method of Claim 269 wherein the detectable change is a color change observable with the naked eye.

274. The method of Claim 273 wherein the color change is observed on a solid surface.

275. The method of Claim 269 wherein the nanoparticles are metal





282. The method of Claim 269 wherein the nucleic acid is a bacterial DNA.

283. The method of Claim 269 wherein the nucleic acid is a fungal DNA.

284. The method of Claim 269 wherein the nucleic acid is a synthetic DNA, a synthetic RNA, a structurally-modified natural or synthetic RNA, or a structurally-modified natural or synthetic DNA.

285. The method of Claim 269 wherein the nucleic acid is from a biological  
10 source.

286. The method of Claim 269 wherein the nucleic acid is a product of a polymerase chain reaction amplification.

15            287.    The method of Claim 269 wherein the nucleic acid is contacted with the  
first and second types of conjugates simultaneously.

288. The method of Claim 269 wherein the nucleic acid is contacted and hybridized with the oligonucleotides on the nanoparticles of first type of conjugates before being contacted with the second type of conjugates.

289. The method of Claim 288 wherein the first type of conjugates is attached to a substrate.

25            290.    The method of Claim 269 wherein the nucleic acid is double-stranded and hybridization with the oligonucleotides on the nanoparticles results in the production of a triple-stranded complex.





portions, and the sequences of the oligonucleotides on the nanoparticles do not include sequences complementary to this third portion of the nucleic acid; and

the nucleic acid is further contacted with a filler oligonucleotide having a sequence complementary to this third portion of the nucleic acid, the contacting taking place under conditions effective to allow hybridization of the filler oligonucleotide with the nucleic acid.

303. The method of Claim 292 wherein the nucleic acid is viral RNA or DNA.

304. The method of Claim 292 wherein the nucleic acid is a gene associated with a disease.

305. The method of Claim 292 wherein the nucleic acid is a bacterial DNA.

306. The method of Claim 292 wherein the nucleic acid is a fungal DNA.

307. The method of Claim 292 wherein the nucleic acid is a synthetic DNA, a synthetic RNA, a structurally-modified natural or synthetic RNA, or a structurally-modified natural or synthetic DNA.

308. The method of Claim 292 wherein the nucleic acid is from a biological source.

309. The method of Claim 292 wherein the nucleic acid is a product of a polymerase chain reaction amplification.

310. The method of Claim 292 wherein the nucleic acid is contacted with the first and second types of nanoparticles simultaneously.

311. The method of Claim 292 wherein the nucleic acid is contacted and hybridized with the oligonucleotides on the first type of nanoparticles before being contacted with the second type of nanoparticles.

5

312. The method of Claim 311 wherein the first type of nanoparticles is attached to a substrate.

313. The method of Claim 292 wherein the nucleic acid is double-stranded and hybridization with the oligonucleotides on the nanoparticles results in the production of a triple-stranded complex.

314. A method of detecting a nucleic acid having at least two portions comprising:

15 providing a type of nanoparticles according to any one of Claims 253-265 having recognition oligonucleotides attached thereto, the recognition oligonucleotides on each nanoparticle comprising a sequence complementary to the sequence of at least two portions of the nucleic acid;

20 contacting the nucleic acid and the nanoparticles under conditions effective to allow hybridization of the recognition oligonucleotides on the nanoparticles with the two or more portions of the nucleic acid; and

observing a detectable change brought about by hybridization of the recognition oligonucleotides on the nanoparticles with the nucleic acid.

25 315. A method of detecting nucleic acid having at least two portions comprising:

contacting the nucleic acid with at least two types of nanoparticles according to any one of Claims 253-263 having recognition oligonucleotides attached







330. The method of Claim 315 wherein the nucleic acid is a synthetic DNA, a synthetic RNA, a structurally-modified natural or synthetic RNA, or a structurally-modified natural or synthetic DNA.

5           331. The method of Claim 315 wherein the nucleic acid is from a biological source.

10           332. The method of Claim 315 wherein the nucleic acid is a product of a polymerase chain reaction amplification.

15           333. The method of Claim 315 wherein the nucleic acid is contacted with the first and second types of nanoparticles simultaneously.

20           334. The method of Claim 315 wherein the nucleic acid is contacted and hybridized with the recognition oligonucleotides on the first type of nanoparticles before being contacted with the second type of nanoparticles.

25           335. The method of Claim 334 wherein the first type of nanoparticles is attached to a substrate.

30           336. The method of Claim 315 wherein the nucleic acid is double-stranded and hybridization with the oligonucleotides on the nanoparticles results in the production of a triple-stranded complex.

35           337. A method of detecting a nucleic acid having at least two portions comprising:

            (a) contacting the nucleic acid with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion

of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

5 (b) contacting said nucleic acid bound to the substrate with a first type of nanoparticle-oligonucleotide conjugates according to any one of Claims 237-240, at least one of the types of oligonucleotides attached to the nanoparticles of the conjugates having a sequence complementary to a second portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides attached to the nanoparticles of the conjugates with said nucleic acid;  
10 and

(c) observing a detectable change.

338. The method of Claim 337 further comprising:

15 (d) contacting the first type of nanoparticle-oligonucleotide conjugates bound to the substrate with a second type of nanoparticle-oligonucleotide conjugates according to any one of Claims 237-240, at least one of the types of oligonucleotides attached to the nanoparticles of the second type of conjugates having a sequence complementary to the sequence of one of the types of oligonucleotides attached to the nanoparticles of the first type of conjugates, the contacting taking place under conditions  
20 effective to allow hybridization of the oligonucleotides attached to the nanoparticles of the first and second types of conjugates; and

(e) observing the detectable change.

25 339. The method of Claim 338 wherein at least one of the types of oligonucleotides on the nanoparticles of the first type of conjugates has a sequence complementary to the sequence of at least one of the types of oligonucleotides on the nanoparticles of the second type of conjugates and the method further comprises:

(f) contacting the second type of conjugates bound to the substrate with

the first type of conjugates, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles of the first and second types of conjugates; and

(g) observing the detectable change.

5

340. The method of Claim 339 wherein step (d) or steps (d) and (f) are repeated one or more times and the detectable change is observed.

341. The method of Claim 337 further comprising:

10

(d) providing a type of binding oligonucleotides having a sequence comprising at least two portions, the first portion being complementary to at least one of the types of oligonucleotides attached to the nanoparticles of the first type of conjugates;

15

(e) contacting the binding oligonucleotides with the first type of conjugates bound to the substrate, the contacting taking place under conditions effective to allow hybridization of the binding oligonucleotides with the oligonucleotides on the nanoparticles of the first type of conjugates;

20

(f) providing a second type of nanoparticle-oligonucleotide conjugates according to any one of Claims 237-240, at least one of the types of oligonucleotides attached to the nanoparticles of the second type of conjugates having a sequence complementary to the second portion of the sequence of the binding oligonucleotides;

25

(g) contacting the binding oligonucleotides bound to the substrate with the second type of conjugates, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides attached to the nanoparticles of the second type of conjugates with the binding oligonucleotides; and

(h) observing the detectable change.

342. The method of Claim 341 further comprising:

(i) contacting the second type of conjugates bound to the substrate with the

binding oligonucleotides, the contacting taking place under conditions effective to allow hybridization of the binding oligonucleotides with the oligonucleotides on the nanoparticles of the second type of conjugates;

5 (j) contacting the binding oligonucleotides bound to the substrate with the first type of conjugates, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles of the first type of conjugates with the binding oligonucleotides; and

(k) observing the detectable change.

10 343. The method of Claim 342 wherein steps (e) and (g) or steps (e), (g), (i) and (j) are repeated one or more times, and the detectable change is observed.

344. The method of Claim 337 wherein the substrate is a transparent substrate or an opaque white substrate.

15 345. The method of Claim 344 wherein the detectable change is the formation of dark areas on the substrate.

20 346. The method of Claim 337 wherein the nanoparticles of the conjugates are metal nanoparticles or semiconductor nanoparticles.

347. The method of Claim 346 wherein the nanoparticles of the conjugates are made of gold or silver.

25 348. The method of Claim 337 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.



oligonucleotides attached to the substrate in the array is located between two electrodes, the nanoparticles are made of a material which is a conductor of electricity, and the detectable change is a change in conductivity.

5           358. The method of Claim 357 wherein the electrodes are made of gold, and the nanoparticles are made of gold.

10           359. The method of Claim 357 wherein the substrate is contacted with silver stain to produce the change in conductivity.

15           360. A method of detecting a nucleic acid having at least two portions comprising:

(a) contacting the nucleic acid with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

(b) contacting said nucleic acid bound to the substrate with a first type of nanoparticles according to any one of Claims 243-250 having one or more types of recognition oligonucleotides attached thereto, at least one of the types of recognition oligonucleotides comprising a sequence complementary to a second portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles with said nucleic acid; and

25           (c) observing a detectable change.

361. The method of Claim 360 further comprising:

(d) contacting the first type of nanoparticles bound to the substrate with a

second type of nanoparticles according to any one of Claims 243-250 having recognition oligonucleotides attached thereto, at least one of the types of recognition oligonucleotides on the second type of nanoparticles comprising a sequence complementary to the sequence of one of the types of oligonucleotides on the first type of nanoparticles, the  
5 contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles; and

(e) observing the detectable change.

362. The method of Claim 360 wherein at least one of the types of recognition  
10 oligonucleotides on the first type of nanoparticles has a sequence complementary to the sequence of at least one of the types of oligonucleotides on the second type of nanoparticles and the method further comprises:

(f) contacting the second type of nanoparticles bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to  
15 allow hybridization of the oligonucleotides on the first and second types of nanoparticles; and

(g) observing the detectable change.

363. The method of Claim 362 wherein step (d) or steps (d) and (f) are repeated  
20 one or more times and the detectable change is observed.

364. The method of Claim 360 further comprising:

(d) providing a type of binding oligonucleotides having a sequence comprising at least two portions, the first portion being complementary to at least one of  
25 the types of oligonucleotides on the first type of nanoparticles;

(e) contacting the binding oligonucleotides with the first type of nanoparticles bound to the substrate, the contacting taking place under conditions effective to allow hybridization of the binding oligonucleotides with the oligonucleotides

on the first type of nanoparticles;

(f) providing a second type of nanoparticles according to any one of Claims 243-250 having recognition oligonucleotides attached thereto, at least one of the types of recognition oligonucleotides on the second type of nanoparticles comprising a sequence complementary to the second portion of the sequence of the binding oligonucleotides;

(g) contacting the binding oligonucleotides bound to the substrate with the second type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the second type of nanoparticles with the binding oligonucleotides; and

(h) observing the detectable change.

365. The method of Claim 364 further comprising:

(i) contacting the second type of nanoparticles bound to the substrate with the binding oligonucleotides, the contacting taking place under conditions effective to allow hybridization of the binding oligonucleotides with the oligonucleotides on the second type of nanoparticles;

(j) contacting the binding oligonucleotides bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first type of nanoparticles with the binding oligonucleotides; and

(k) observing the detectable change.

366. The method of Claim 365 wherein steps (e) and (g) or steps (e), (g), (i) and (j) are repeated one or more times, and the detectable change is observed.

367. The method of Claim 360 wherein the substrate is a transparent substrate or an opaque white substrate.





acid detected.

378. The method of Claim 360 wherein the oligonucleotides attached to the substrate are located between two electrodes, the nanoparticles are made of a material  
5 which is a conductor of electricity, and the detectable change is a change in conductivity.

379. The method of Claim 378 wherein the electrodes are made of gold, and the nanoparticles are made of gold.

10 380. The method of Claim 378 wherein the substrate is contacted with silver stain to produce the change in conductivity.

381. The method of Claim 371 wherein each of the plurality of oligonucleotides attached to the substrate in the array is located between two electrodes,  
15 the nanoparticles are made of a material which is a conductor of electricity, and the detectable change is a change in conductivity.

382. The method of Claim 381 wherein the electrodes are made of gold, and the nanoparticles are made of gold.  
20

383. The method of Claim 381 wherein the substrate is contacted with silver stain to produce the change in conductivity.

384. A method of detecting a nucleic acid having at least two portions  
25 comprising:

(a) contacting the nucleic acid with a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under conditions

effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

(b) contacting said nucleic acid bound to the substrate with a first type of nanoparticles according to any one of Claims 253-263 having one or more types of recognition oligonucleotides attached thereto, at least one of the types of recognition oligonucleotides comprising a sequence complementary to a second portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the recognition oligonucleotides on the nanoparticles with said nucleic acid; and

(c) observing a detectable change.

385. The method of Claim 384 further comprising:

(d) contacting the first type of nanoparticles bound to the substrate with a second type of nanoparticles according to any one of Claims 253-263 having recognition oligonucleotides attached thereto, at least one of the types of recognition oligonucleotides on the second type of nanoparticles comprising a sequence complementary to the sequence of one of the types of oligonucleotides on the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles; and

(e) observing the detectable change.

386. The method of Claim 385 wherein at least one of the types of recognition oligonucleotides on the first type of nanoparticles comprises a sequence complementary to the sequence of at least one of the types of oligonucleotides on the second type of nanoparticles and the method further comprises:

(f) contacting the second type of nanoparticles bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles;

and

(g) observing the detectable change.

387. The method of Claim 386 wherein step (d) or steps (d) and (f) are repeated  
5 one or more times and the detectable change is observed.

388. The method of Claim 384 further comprising:

(d) providing a type of binding oligonucleotides having a sequence  
comprising at least two portions, the first portion being complementary to at least one of  
10 the types of oligonucleotides on the first type of nanoparticles;

(e) contacting the binding oligonucleotides with the first type of  
nanoparticles bound to the substrate, the contacting taking place under conditions  
effective to allow hybridization of the binding oligonucleotides with the oligonucleotides  
on the first type of nanoparticles;

15 (f) providing a second type of nanoparticles according to any one of  
Claims 253-263 having recognition oligonucleotides attached thereto, at least one of the  
types of recognition oligonucleotides on the second type of nanoparticles comprising a  
sequence complementary to the second portion of the sequence of the binding  
oligonucleotides;

20 (g) contacting the binding oligonucleotides bound to the substrate with the  
second type of nanoparticles, the contacting taking place under conditions effective to  
allow hybridization of the oligonucleotides on the second type of nanoparticles with the  
binding oligonucleotides; and

(h) observing the detectable change.

25

389. The method of Claim 388 further comprising:

(i) contacting the second type of nanoparticles bound to the substrate with  
the binding oligonucleotides, the contacting taking place under conditions effective to

allow hybridization of the binding oligonucleotides with the oligonucleotides on the second type of nanoparticles;

(j) contacting the binding oligonucleotides bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first type of nanoparticles with the binding oligonucleotides; and

(k) observing the detectable change.

390. The method of Claim 389 wherein steps (e) and (g) or steps (e), (g), (i) and (j) are repeated one or more times, and the detectable change is observed.

391. The method of Claim 384 wherein the substrate is a transparent substrate or an opaque white substrate.

392. The method of Claim 391 wherein the detectable change is the formation of dark areas on the substrate.

393. The method of Claim 384 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

394. The method of Claim 393 wherein the nanoparticles are made of gold or silver.

395. The method of Claim 384 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

396. The method of Claim 384 wherein the substrate is contacted with silver





them.

409. The method of Claim 407 wherein the nanoparticles are made of metal.

5           410. The method of Claim 407 wherein the nanoparticles are made of gold or silver.

10           411. The method of Claim 407 wherein the substrate is contacted with silver stain to produce the change in conductivity.

15           412. The method of Claim 407 further comprising:

(d) contacting the first type of nanoparticles bound to the substrate with a second type of nanoparticles, the nanoparticles being made of a material which can conduct electricity, the nanoparticles having oligonucleotides attached thereto, at least one of the types of oligonucleotides on the second type of nanoparticles comprising a sequence complementary to the sequence of one of the types of oligonucleotides on the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles; and

20           (e) detecting the change in conductivity.

25           413. The method of Claim 412 wherein at least one of the types of oligonucleotides on the first type of nanoparticles has a sequence complementary to the sequence of at least one of the types of oligonucleotides on the second type of nanoparticles and the method further comprises:

(f) contacting the second type of nanoparticles bound to the substrate with the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the first and second types of nanoparticles; and



(g) detecting the change in conductivity.

414. The method of Claim 413 wherein step (d) or steps (d) and (f) are repeated one or more times and the change in conductivity is detected.

5

415. The method of Claim 407 further comprising:

(d) contacting the first type of nanoparticles bound to the substrate with an aggregate probe having oligonucleotides attached thereto, the nanoparticles of the aggregate probe being made of a material which can conduct electricity, at least one of the types of oligonucleotides on the aggregate probe comprising a sequence complementary to the sequence of one of the types of oligonucleotides on the first type of nanoparticles, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the aggregate probe with the oligonucleotides on the first type of nanoparticles;

(e) and detecting the change in conductivity.

416. A method of detecting nucleic acid having at least two portions comprising:

(a) contacting a nucleic acid with a substrate having oligonucleotides attached thereto, the oligonucleotides being located between a pair of electrodes, the oligonucleotides having a sequence complementary to a first portion of the sequence of said nucleic acid, the contacting taking place under conditions effective to allow hybridization of the oligonucleotides on the substrate with said nucleic acid;

(b) contacting said nucleic acid bound to the substrate with an aggregate probe having oligonucleotides attached thereto, at least one of the types of oligonucleotides on the aggregate probe comprising a sequence complementary to the sequence of a second portion of said nucleic acid, the nanoparticles of the aggregate probe being made of a material which can conduct electricity, the contacting taking place

under conditions effective to allow hybridization of the oligonucleotides on the aggregate probe with the nucleic acid; and

(c) detecting a change in conductivity.

5           417. A method of detecting a nucleic acid wherein the method is performed on a substrate, the method comprising detecting the presence, quantity, or both, of the nucleic acid with an optical scanner.

10           418. The method of Claim 417 wherein the device is a flatbed scanner.

15           419. The method of Claim 417 wherein the scanner is linked to a computer loaded with software capable of calculating greyscale measurements, and the greyscale measurements are calculated. to provide a quantitative measure of the amount of nucleic acid detected.

20           420. The method of Claim 417 wherein the scanner is linked to a computer loaded with software capable of providing an image of the substrate, and a qualitative determination of the presence of the nucleic acid, the quantity of the nucleic acid, or both, is made.

          421. A kit comprising a container holding nanoparticle-oligonucleotide conjugates according to any one of Claims 237-242.

25           422. A kit comprising a container holding nanoparticles according to any one of Claims 243-265.

          423. A kit comprising a substrate having attached thereto at least one pair of electrodes with oligonucleotides attached to the substrate between the electrodes.







to allow hybridization of the oligonucleotides on the nanoparticles with the selected nucleic acid so that the nanoparticles hybridized to the selected nucleic acid aggregate and precipitate.

5           433. Nanoparticle-oligonucleotide conjugates which are nanoparticles having oligonucleotides attached to them, the oligonucleotides having a covalently bound cyclic disulfide functional group that can bind to the nanoparticles.

10           434. Nanoparticle-oligonucleotide conjugates which are nanoparticles having oligonucleotides attached to them, the oligonucleotides having a covalently bound polythiol functional group that can bind to the nanoparticles.

15           435. Nanoparticle-oligonucleotide conjugates which are nanoparticles having oligonucleotides attached to them, the oligonucleotides having a covalently bound cyclic disulfide functional group that can bind to the nanoparticles, at least some of the oligonucleotides having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

20           436. Nanoparticle-oligonucleotide conjugates which are nanoparticles having oligonucleotides attached to them, the oligonucleotides having a covalently bound polythiol functional group that can bind to the nanoparticles, at least some of the oligonucleotides having a sequence complementary to at least one portion of the sequence of a nucleic acid or another oligonucleotide.

25           437. The conjugates of claims 435 or 436 wherein the oligonucleotides are further present at a surface density sufficient so that the conjugates are stable.

438. The conjugates of claim 437 wherein the oligonucleotides are present on







contacting the oligonucleotides and the nanoparticles under conditions effective to allow at least some of the oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

5           454. A method of binding oligonucleotides to nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

          providing oligonucleotides having covalently bound polythiol function groups that can bind to nanoparticles; and

          contacting the oligonucleotides and the nanoparticles under conditions  
10       effective to allow at least some of the oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

          455. The method of claims 454 or 455 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

15

          456. The method of claim 455 wherein the nanoparticles are gold nanoparticles.

          457. The method of claims 453 or 454 wherein, the oligonucleotides comprising at least one type of recognition oligonucleotides, each of the recognition  
20       oligonucleotides comprising a spacer portion and a recognition portion, the spacer portion having a moiety covalently bound thereto, the moiety comprising a functional group which can bind to the nanoparticles.

          458. The method of claim 457 wherein the spacer portion comprises at least  
25       about 10 nucleotides.

          459. The method of claims 458 wherein the spacer portion comprises from about 10 to about 30 nucleotides.

460. The method of claims 459 wherein the bases of the nucleotides of the spacer are all adenines, all thymines, all cytosines, all uracils, or all guanines.

5           461. The method of claim 457, wherein the oligonucleotides further comprising a type of diluent oligonucleotides and contacting the oligonucleotides with the nanoparticles under conditions effective to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

10

462. The method of claim 461 wherein the diluent oligonucleotides contain about the same number of nucleotides as are contained in the spacer portions of the recognition oligonucleotides.

15

463. The method of claim 462 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

20           464. The method of claim 457 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

465. A method of binding oligonucleotides to charged nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

25           providing oligonucleotides having covalently bound cyclic disulfide function groups that can bind to nanoparticles, the oligonucleotides comprising:

          a type of recognition oligonucleotides; and

          a type of diluent oligonucleotides;

          contacting the oligonucleotides with the nanoparticles in water for a period

of time sufficient to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles;

adding at least one salt to the water to form a salt solution, the ionic strength of the salt solution being sufficient to overcome at least partially the electrostatic attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic repulsion of the oligonucleotides for each other; and

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow additional oligonucleotides of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

466. A method of binding oligonucleotides to charged nanoparticles to produce nanoparticle-oligonucleotide conjugates, the method comprising:

providing oligonucleotides having covalently bound polythiol function groups that can bind to nanoparticles, the oligonucleotides comprising:

a type of recognition oligonucleotides; and

a type of diluent oligonucleotides;

contacting the oligonucleotides with the nanoparticles in water for a period of time sufficient to allow at least some of each of the types of oligonucleotides to bind to the nanoparticles;

adding at least one salt to the water to form a salt solution, the ionic strength of the salt solution being sufficient to overcome at least partially the electrostatic attraction or repulsion of the oligonucleotides for the nanoparticles and the electrostatic repulsion of the oligonucleotides for each other; and

contacting the oligonucleotides and nanoparticles in the salt solution for an additional period of time sufficient to allow additional oligonucleotides of each of the types of oligonucleotides to bind to the nanoparticles to produce the nanoparticle-oligonucleotide conjugates.

467. The method of claims 465 or 466 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

5           468. The method of claims 467 wherein the nanoparticles are gold nanoparticles.

10           469. The method of claims 465 or 466 wherein all of the salt is added to the water in a single addition.

15           470. The method of claims 465 or 466 wherein the salt is added gradually over time.

20           471. The method of claims 465 or 466 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium, chloride, sodium, acetate, ammonium acetate, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more these salts in a phosphate buffer.

25           472. The method of claim 471 wherein the salt is sodium chloride in a phosphate buffer.

            473. The method of claims 465 or 466 wherein nanoparticle-oligonucleotide conjugates are produced which have the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 10 picomoles/cm<sup>2</sup>.

            474. The method of claim 473 wherein the oligonucleotides are present on surface of the nanoparticles at a surface density of at least 15 picomoles/cm<sup>2</sup>.



482. The method of claim 481 wherein the sequence of the diluent oligonucleotides is the same as the sequence of the spacer portions of the recognition oligonucleotides.

5           483. The method of claims 476 or 477 wherein the oligonucleotides comprise at least two types of recognition oligonucleotides.

10           484. Oligonucleotides having a covalently bound cyclic disulfide functional group that can bind to the nanoparticles.

          485. Oligonucleotides having a covalently bound polythiol functional group that can bind to the nanoparticles.

15           486. The compositions according to claims 433, 435, 445, 446, 453, 465, and 484 wherein a large hydrophobic group is located between the oligonucleotide and the cyclic disulfide functional group.

          487. A method for detecting an analyte in a sample comprising:  
          providing a type of nanoparticle conjugate having oligonucleotides bound thereto,  
20   at least a portion of the oligonucleotides attached to the nanoparticles are bound, as a result of hybridization, to second oligonucleotides having a specific binding complement of said analyte bound thereto;

          contacting the analyte with the nanoparticle conjugate under conditions effective to allow specific binding interactions between the analyte and specific binding  
25   complement bound to the nanoparticle conjugate; and

          observing a detectable change brought about by the specific binding interaction of the analyte and the specific binding complement of said analyte.

488. A method for detecting an analyte comprising:

providing a type of nanoparticle conjugate having oligonucleotides bound thereto,  
at least a portion of the oligonucleotides attached to the nanoparticles are bound, as a  
result of hybridization, to a first portion of a linker oligonucleotide, the linker  
5 oligonucleotide having a second portion that is bound, as a result of hybridization, to  
oligonucleotides having bound thereto a specific binding complement of said analyte;

contacting the analyte with a nanoparticle conjugate under conditions effective to  
allow specific binding interaction between the analyte and specific binding complement  
bound to the nanoparticle conjugate; and

10 observing a detectable change brought about by the specific binding interaction of  
the analyte and the specific binding complement of said analyte.

489. A method for detecting an analyte comprising:

providing (i) an analyte having an oligonucleotide bound thereto, (ii) a first type  
15 of nanoparticles having oligonucleotides bound thereto, the oligonucleotides bound to the  
first type of nanoparticles having a sequence that is complementary to the sequence of the  
oligonucleotide bound to the analyte, and (iii) a second type of nanoparticle conjugate  
having oligonucleotides bound thereto, a portion of the oligonucleotides bound to the  
second type of nanoparticle are bound, as a result of hybridization, to oligonucleotides  
20 having bound thereto a specific binding complement of said analyte;

contacting the oligonucleotide bound to the analyte with the first type of  
nanoparticles under conditions effective to allow hybridization between the  
oligonucleotides bound to the analyte with the oligonucleotides attached to the first type  
of nanoparticles to form a nanoparticle analyte conjugate;

25 contacting the nanoparticle analyte conjugate with a second type of nanoparticle  
conjugates under conditions effective to allow specific binding interaction between the  
analyte and specific binding complement of the second type of nanoparticle conjugate;  
and

observing a detectable change brought about by the specific binding interaction of the analyte and the specific binding complement of said analyte.

490. A method for detecting an analyte comprising:

- 5 providing (ii) a linker oligonucleotide, the linker oligonucleotide having at least two portions, (iii) a first type of nanoparticle have oligonucleotides attached thereto, a least a portion of the oligonucleotides bound to the first type of nanoparticles have a sequence that is complementary to a second portion of the linker oligonucleotide; (i) an analyte having an oligonucleotide bound thereto, the oligonucleotide having a sequence  
10 complementary to the first portion of the linker oligonucleotide; and (iv) a second type of nanoparticles having oligonucleotides bound thereto, at least a portion of the oligonucleotides bound to the second type of nanoparticles are bound, as a result of hybridization, to an oligonucleotide having bound thereto a specific binding complement of the analyte;
- 15 contacting the linker oligonucleotide with the first type of nanoparticles under conditions effective to allow hybridization between the oligonucleotide attached to the first type of nanoparticles with a first portion of the linker oligonucleotide;
- contacting the linker oligonucleotide with the oligonucleotide having the analyte bound thereto under conditions effective to allow hybridization between the  
20 oligonucleotide having analyte bound thereto with a second portion of the linker oligonucleotide;
- contacting the analyte bound to the first type of nanoparticles with a second type of nanoparticles under conditions effective to allow specific binding interactions between the analyte bound to the first type of nanoparticles and the specific binding complement  
25 bound to the second type of nanoparticles; and
- observing the detectable change brought about by the specific binding of the analyte to the specific binding complement of the analyte.





binding complement of said analyte;

contacting the analyte bound to the support to the nanoparticle conjugate under conditions effective to allow specific binding interactions between the analyte and specific binding complement bound to the nanoparticle conjugate; and

5        observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.

500.    A method for detecting an analyte comprising:

providing (i) a support having a oligonucleotides bound thereto, (ii) an analyte  
10    having an oligonucleotide bound thereto, the oligonucleotide bound to the analyte has a sequence that is complementary to the oligonucleotides bound to the support; and (iii) a type of nanoparticle conjugate having oligonucleotides bound thereto, at least a portion of the oligonucleotides bound to the nanoparticle are bound, as a result of hybridization, to second oligonucleotides having bound thereto a specific binding complement of said  
15    analyte;

contacting the oligonucleotides bound to the support with the oligonucleotide bound to the analyte under conditions effective to allow hybridization between the oligonucleotides bound to the support and the oligonucleotides bound to the analytes;

contacting the analyte bound to the support with the nanoparticle conjugate under  
20    conditions effective to allow for specific binding interactions between the analyte bound to the support and the specific binding complement bound to the nanoparticle; and

observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.

25        501.    A method for detecting an analyte in a sample comprising:

providing (i) a support having oligonucleotides bound thereto, (ii) a linker oligonucleotide, (ii) an analyte having an oligonucleotide bound thereto,(iii) a type of nanoparticle conjugate having oligonucleotides bound thereto, wherein at least a portion

- of the oligonucleotides bound to the nanoparticle conjugate are bound, as a result of hybridization, to oligonucleotides having bound thereto a specific binding complement of said analyte, the sequence of the linker oligonucleotide having at least two portions, the oligonucleotides bound to the support have a sequence that is complementary to the first
- 5 portion of the linker oligonucleotide, the oligonucleotide bound to the analyte has a sequence that is complementary to the second portion of the linker oligonucleotides;
- contacting the linker oligonucleotide with the oligonucleotide bound to the support under conditions effective to allow hybridization between the oligonucleotides bound to the support with the first portion of the linker oligonucleotide;
- 10 contacting the linker oligonucleotide with the oligonucleotide bound to the analyte under conditions effective to allow hybridization between the oligonucleotide bound to the analyte and the second portion of the linker oligonucleotide;
- contacting analyte bound to the support with the nanoparticle conjugate under conditions effective to allow specific binding interaction between the analyte bound to
- 15 the support and the specific binding complement bound to the nanoparticle conjugate; and
- observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.
- 20 502. A method for detecting an analyte comprising:
- providing (i) a support having oligonucleotides bound thereto, (ii) an analyte having oligonucleotides bound thereto, the sequence of the oligonucleotide bound to the analyte is complementary to the sequence of the oligonucleotides bound the support; (iii)
- 25 a type of nanoparticles having oligonucleotides bound thereto, at least a portion of the oligonucleotides attached to the nanoparticle are bound, as a result of hybridization, to a first portion of a linker oligonucleotide, a second portion of the linker oligonucleotide is further bound, as a result of hybridization, to an oligonucleotide having a oligonucleotide having bound thereto a specific binding complement of said analyte;

contacting the oligonucleotides bound to the support with oligonucleotide bound to an analyte under conditions effective to allow hybridization between the oligonucleotides bound to the support with the oligonucleotides bound to the analyte;

5 contacting the analyte bound to the support with the the nanoparticle conjugate under conditions effective to allow specific binding interactions between the analyte bound to the support and the specific binding complement bound to the nanoparticle; and observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.

10 503. A method for detecting an analyte comprising:  
providing (i) a support having an analyte bound thereto, (ii) an aggregate probe comprising at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, and at least one of the  
15 types of nanoparticles of the aggregate probe have oligonucleotides attached thereto which are bound, as a result of hybridization, to second oligonucleotides having bound thereto a specific binding complement of said analyte;

contacting the support with the aggregate probe under conditions effective to allow specific binding interactions between the analyte bound to the support and specific  
20 binding complement bound to the aggregate probe; and

observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.

504. A method for detecting an analyte comprising:  
25 providing (i) a support having an oligonucleotide bound thereto; (ii) an analyte having an oligonucleotide bound thereto, the oligonucleotide bound to the analyte has a sequence that is complementary to the sequence of the oligonucleotides bound to the support, (iii) an aggregate probe comprising at least two types of nanoparticles having

oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, and at least one of the types of nanoparticles of the aggregate probe have oligonucleotides attached thereto which are bound, as a result of hybridization, to second

5 oligonucleotides having bound thereto a specific binding complement of said analyte;

contacting a support having oligonucleotides bound thereto with the analyte having an oligonucleotide bound thereto. The contacting occurs under conditions effective to allow hybridization of the oligonucleotides bound to the analyte with the oligonucleotides bound to the support; and

10 contacting the analyte bound to the support with an aggregate probe under conditions effective to allow specific binding interactions between the analyte bound to the support and specific binding complement bound to the aggregate probe; and

observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.

15

505. A method for detecting an analyte comprising:

providing (i) a support having a oligonucleotides bound thereto, (ii) a linker oligonucleotide having at least two portions,(iii) an analyte having oligonucleotides bound thereto, (iv) an aggregate probe comprising at least two types of nanoparticles

20 having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them, at least one of the types of nanoparticles of the aggregate probe have some oligonucleotides attached thereto which bound, as a result of hybridization, to second oligonucleotides having bound thereto a specific binding complement of said

25 analyte, the oligonucleotides bound to the support has a sequence that is complementary to a first portion of the linker oligonucleotide, the oligonucleotide bound to the analyte has a sequence that is complementary with the second portion of the linker oligonucleotide;

contacting the linker oligonucleotide with the oligonucleotides bound to the support under conditions effective to allow hybridization between the oligonucleotides bound to the support and the first portion of the linker oligonucleotide;

contacting the linker oligonucleotide with the oligonucleotide bound to the  
5 analyte under conditions effective to allow hybridization between the second portion of  
the linker oligonucleotide bound to the support and the oligonucleotide bound to the  
analyte;

contacting the analyte bound to the support with the aggregate probe under conditions effective to allow specific binding interactions between the analyte bound to the support and specific binding complement bound to the aggregate probe; and

observing a detectable change dependent on the specific binding of the analyte to the specific binding complement of the analyte.

506. A method for detecting an analyte comprising:

15 providing (i) a support having oligonucleotides bound thereto, (ii) an analyte having oligonucleotide bound thereto, the oligonucleotide has a sequence that is complementary to the sequence of the oligonucleotides bound to the support, (iii) an aggregate probe comprising at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result  
20 of the hybridization of some of the oligonucleotides attached to them and at least one of the types of nanoparticles of the aggregate probe have some oligonucleotides attached thereto which bound to a first portion of a linker oligonucleotide as a result of hybridization, a second portion of the second linker oligonucleotide is bound, as a result of hybridization, to a oligonucleotide having bound thereto a specific binding  
25 complement of said analyte;

contacting a support having oligonucleotides bound thereto with an oligonucleotide having analyte bound thereto under conditions effective to allow hybridization of the oligonucleotides bound to the analyte with the oligonucleotides









5       observing the detectable change resulting from the specific binding of biotin with streptavidin or avidin.

512. The method according to claim 511, wherein the sbp member is biotin.

10            513. The method according to claim 511, wherein the sb complement is streptavidin or avidin.

514. A method for detecting a nucleic acid comprising:  
providing a support having oligonucleotides bound thereto, the oligonucleotides  
15 bound to the support have a sequence that is complementary to the first portion of the  
nucleic acid;

contacting the nucleic acid with a support having oligonucleotides bound thereto under conditions effective to allow hybridization between the oligonucleotides bound to the support with the first portion of the nucleic acid;

20 providing an oligonucleotide having a sbp member bound thereto, the oligonucleotide bound to the sbp member has a sequence that is complementary to the second portion of the nucleic acid;

contacting the nucleic acid bound to the support with the oligonucleotide bound to the sbp member under conditions effective to allow hybridization between the

25 oligonucleotide bound to the sbp member and the second portion of the nucleic acid;

providing a type of nanoparticle conjugate having oligonucleotides bound thereto, at least a portion of the oligonucleotides bound to the nanoparticle conjugate are bound, as a result of hybridization, to oligonucleotides having bound thereto a specific binding

complement of said sbp member;

contacting the sbp member bound to the support with the nanoparticle conjugate under conditions effective to allow specific binding interaction between the sbp member bound to the support and the specific binding complement bound to the nanoparticle; and

5        observing a detectable change dependent on the specific binding of the sbp member and the specific binding complement.

515.    The method according to claim 514, wherein the sbp member is streptavidin or avidin.

10

516.    The method according to claim 514, wherein the sb complement is biotin.

517.    A method for detecting a nucleic acid comprising:

15        providing a nanoparticle conjugate having oligonucleotides attached thereto, at least some of the oligonucleotides attached to the nanoparticles have a sequence that is complementary to the first portion of the nucleic acid;

          contacting a nucleic acid with the oligonucleotides bound to the nanoparticle conjugate under conditions effective to allow hybridization of the oligonucleotides bound to the nanoparticles with the first portion of the nucleic acid;

20        providing an oligonucleotide having sbp member bound thereto, the oligonucleotide bound to the sbp member has a sequence that is complementary to the second portion of the nucleic acid;

          contacting the nucleic acid with the oligonucleotide having the sbp member under conditions effective to allow hybridization between the oligonucleotide having the sbp member and the nucleic acid;

25

          providing a support having bound thereto a specific binding complement of the sbp member;

          contacting the support with the sbp member bound to the nanoparticle under



some oligonucleotides attached thereto which bound, as a result of hybridization, to oligonucleotides having bound thereto a specific binding complement of said sbp member;

- 5       contacting the sbp member bound to the support with the aggregate probe under conditions effective to allow specific binding interactions between the sbp member bound to the support and specific binding complement bound to the aggregate probe; and  
      observing a detectable change dependent on the specific binding of the sbp member and the sb complement of the sbp member.

10       521.   The method according to claim 520, wherein the sbp member is biotin.

      522.   The method according to claim 520, wherein the sb complement is strepavidin or avidin.

15       523.   A method for detecting a nucleic acid comprising:  
      providing (i) an aggregate probe comprising at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them and at least one of the types of nanoparticles of the aggregate probe have  
20   some oligonucleotides attached thereto which are complementary to a first portion of the nucleic acid, and (ii) an oligonucleotide having sbp member, the oligonucleotide having an sbp member bound thereto has a sequence that is complementary to the second portion of the nucleic acid;

      contacting the nucleic acid with an aggregate probe under conditions effective to  
25   allow hybridization between a portion of the oligonucleotides bound to the aggregate probe with the first portion of the nucleic acid under conditions effective to allow hybridization between the oligonucleotides bound to the aggregate probe with the first portion of the nucleic acid;



detectable change is the formation of dark areas on the substrate.

529. The method according to any one of Claims 499-525, wherein the nanoparticles are made of gold.

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530. The method according to any one of Claims 498-523, wherein the substrate is contacted with silver stain to produce the detectable change.

531 The method according to any one of Claims 498-523, wherein the  
10 detectable change is observed with an optical scanner.

532. A nanoparticle conjugate for detecting an analyte comprising:  
(i) nanoparticles having oligonucleotides bound thereto; and  
(ii) oligonucleotide having bound thereto a specific binding complement of an  
15 analyte, the oligonucleotides having the specific binding complement bound thereto have a sequence that is complementary to at least a portion of the oligonucleotides bound to the nanoparticles and are bound, as a result of hybridization, to at least a portion of the oligonucleotides bound to the nanoparticles.

533. A nanoparticle conjugate for detecting an analyte comprising:  
(i) nanoparticles having oligonucleotides bound thereto;  
(ii) oligonucleotide having bound thereto a specific binding complement of an  
20 analyte member; and  
(iii) a linker oligonucleotide having at least two portions, a first portion of the  
25 linker oligonucleonucleotide is bound, as a result of hybridization, to the oligonucleotides bound to the nanoparticle and a second portion of the linker oligonucleotide is bound, as a result of hybridization, to the oligonucleotides having bound thereto a specific binding complement of an analyte.

534. An aggregate probe for detecting an analyte comprising:

- 5 (i) at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them; and
- (ii) oligonucleotides having bound thereto a specific binding complement of an analyte, the oligonucleotides having the specific binding complement bound thereto are bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe.

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535. An aggregate probe for detecting an analyte comprising:

- (i) at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them;
- 15 (ii) oligonucleotides having bound thereto a specific binding complement of an analyte; and
- (iii) a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleotide is bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and a second portion of
- 20 the linker oligonucleotide is bound, as a result of hybridization, to the oligonucleotides having bound thereto a specific binding complement of an analyte.

536. A method for preparing a nanoprobe conjugate for detecting an analyte comprising:

- 25 providing (i) a nanoparticle conjugate having oligonucleotides bound thereto and (ii) oligonucleotides having bound thereto a specific binding complement of an analyte, at least a portion of the oligonucleotides bound to the nanoparticles have a sequence that is complementary to the sequence of the oligonucleotides bound to the specific binding



complement, and

contacting the oligonucleotides attached to the nanoparticle conjugate with the oligonucleotides bound to the specific binding complement under conditions effective to allow hybridization between the oligonucleotides bound to the nanoparticles with the  
5 oligonucleotides bound to the specific binding complement.

537. A kit for detecting an analyte comprising

- (a) at least one container holding nanoparticle conjugates comprising (i) nanoparticles having oligonucleotides bound thereto; and (ii) oligonucleotide having  
10 bound thereto a specific binding complement of an analyte, the oligonucleotides having the specific binding pair member have a sequence that is complementary to at least a portion of the oligonucleotides bound to the nanoparticles and are bound, as a result of hybridization, to at least a portion of the oligonucleotides bound to the nanoparticles; and  
15 (b) an optional support for observing a detectable change.

538. A kit for detecting an analyte comprising

- (a) at least one container holding nanoparticle conjugates comprising  
(i) nanoparticles having oligonucleotides bound thereto;  
(ii) oligonucleotide having bound thereto a specific binding complement of an  
20 analyte member; and  
(iii) a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleonucleotide is bound, as a result of hybridization, to the oligonucleotides bound to the nanoparticle and a second portion of the linker oligonucleotide is bound, as a result of hybridization, to the oligonucleotides having bound thereto a specific binding  
25 complement of an analyte; and  
(b) an optional support for observing a detectable change.

539. A kit for detecting an analyte comprising

(b) at least one container holding aggregate probes comprising

(i) at least two types of nanoparticles having oligonucleotides bound thereto, nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them; and

5 (ii) oligonucleotides having bound thereto a specific binding complement of an analyte, the oligonucleotides having the specific binding complement bound thereto are bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and

(b) an optional support for observing a detectable change.

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540. A kit for detecting an analyte comprising

(a) at least one container holding aggregate probes comprising

(i) at least two types of nanoparticles having oligonucleotides bound thereto, nanoparticles of the aggregate probe are bound to each other as a result of the

15 hybridization of some of the oligonucleotides attached to them;

(ii) oligonucleotides having bound thereto a specific binding complement of  
 yte; and

(iii) a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleotide is bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and a second portion of the linker oligonucleotide is bound, as a result of hybridization, to the oligonucleotides having bound thereto a specific binding complement of an analyte; and

(b) an optional support for observing a detectable change.

25            541.    A kit for detecting an analyte comprising:

(a) at least one container holding a type of nanoparticle conjugates comprising nanoparticles having oligonucleotides bound thereto;

(b) a container holding oligonucleotide having bound thereto a specific

binding complement of an analyte, the oligonucleotides having bound thereto the specific binding pair member have a sequence that is complementary to at least a portion of the oligonucleotides bound to the nanoparticles; and

- (c) an optional support for observing a detectable change.

5

542. A kit for detecting an analyte comprising

- (a) at least one container holding nanoparticle conjugates comprising nanoparticles having oligonucleotides bound thereto;

- (b) a container holding oligonucleotide having bound thereto a specific binding complement of an analyte member;

- (c) a container holding a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleotide is complementary to at least a portion of the oligonucleotides bound to the nanoparticle and a second portion of the linker oligonucleotide is complementary to the oligonucleotides having bound thereto a specific binding complement of an analyte; and

15

- (d) an optional support for observing a detectable change.

543. A kit for detecting an analyte comprising

- (a) at least one container holding aggregate probes comprising at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them;

20

- (b) a container holding oligonucleotides having bound thereto a specific binding complement of an analyte, the oligonucleotides having bound thereto the specific binding complement are complementary to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and

25

- (c) an optional support for observing a detectable change.

544. A kit for detecting an analyte comprising

(a) at least one container holding aggregate probes comprising at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them;

(b) a container holding oligonucleotides having bound thereto a specific binding complement of an analyte;

(c) a container holding a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleonucleotide has a sequence that is complementary to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and a second portion of the linker oligonucleotide has a sequence that is complementary to the oligonucleotides having bound thereto a specific binding complement of an analyte; and

(d) an optional support for observing a detectable change.

545. A kit for detecting an analyte comprising:

(a) at least one container holding a type of nanoparticle conjugates comprising nanoparticles having oligonucleotides bound thereto;

(b) a container holding oligonucleotide having covalently bound thereto a functional group for binding a specific binding complement of an analyte, the oligonucleotides having the bound functional group have a sequence that is complementary to at least a portion of the oligonucleotides bound to the nanoparticles; and

(c) an optional support for observing a detectable change.

546. A kit for detecting an analyte comprising

(a) at least one container holding nanoparticle conjugates comprising nanoparticles having oligonucleotides bound thereto;

547. A kit for detecting an analyte comprising

(a) at least one container holding aggregate probes comprising at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them;

(b) a container holding oligonucleotide having covalently bound thereto a functional group for binding a specific binding complement of an analyte, the oligonucleotides having the functional group have a sequence that is complementary to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and

(c) an optional support for observing a detectable change.

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first portion of the linker oligonucleonucleotide has a sequence that is complementary to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and a second portion of the linker oligonucleotide has a sequence that is complementary to the oligonucleotides having the functional group bound thereto; and

5 (d) an optional support for observing a detectable change.

549. A kit for detecting an analyte comprising:

a substrate having oligonucleotides attached thereto;

an oligonucleotide having a covalently bound thereto a functional group

10 for binding a specific binding complement of an analyte, the oligonucleotide bound to the functional group having a sequence that is complementary to the oligonucleotides bound to the substrate; and

a nanoparticle conjugate comprising (i) nanoparticles having

oligonucleotides bound thereto; and (ii) oligonucleotide having bound thereto a specific  
15 binding complement of an analyte, the oligonucleotides having bound thereto the specific binding complement have a sequence that is complementary to at least a portion of the oligonucleotides bound to the nanoparticles and are bound, as a result of hybridization, to at least a portion of the oligonucleotides bound to the nanoparticles.

20 550. A kit for detecting an analyte comprising:

a substrate having oligonucleotides attached thereto;

an oligonucleotide having a covalently bound thereto a functional group

for binding a specific binding complement of an analyte, the oligonucleotide bound to the functional group having a sequence that is complementary to the oligonucleotides  
25 bound to the substrate; and

nanoparticle conjugates comprising (i) nanoparticles having

oligonucleotides bound thereto; (ii) oligonucleotide having bound thereto a specific binding complement of the sbp member; and (iii) a linker oligonucleotide having at least



a oligonucleotide having an sbp member bound thereto, the oligonucleotide having the bound sbp member having a sequence that is complementary to a second portion of the nucleic acid; and

nanoparticle conjugates comprising (i) nanoparticles having oligonucleotides  
5 bound thereto; (ii) oligonucleotide having bound thereto a specific binding complement  
of the sbp member; and (iii) a linker oligonucleotide having at least two portions, a first  
portion of the linker oligonucleotide is bound, as a result of hybridization, to the  
oligonucleotides bound to the nanoparticle and a second portion of the linker  
oligonucleotide is bound, as a result of hybridization, to the oligonucleotides having  
10 bound thereto a specific binding complement of an analyte.

555. The kit according to claim 554, wherein the sbp member is biotin.

556. The kit according to claim 554, wherein the specific binding complement  
15 of the sbp member is streptavidin or avidin.

557. A kit for detecting an analyte comprising:  
a substrate having oligonucleotides attached thereto;  
an oligonucleotide having a covalently bound thereto a functional group for  
20 binding an analyte, the oligonucleotide bound to the functional group having a sequence  
that is complementary to the oligonucleotides bound to the substrate; and

an aggregate probe comprising: (i) at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them; and (ii) oligonucleotides having bound thereto a specific binding complement of an analyte, the oligonucleotides having bound thereto a specific binding complement of an analyte are further bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe.



558. A kit for detecting an analyte comprising:

a substrate having oligonucleotides attached thereto;

an oligonucleotide having a covalently bound thereto a functional group for

5 binding an analyte, the oligonucleotide bound to the functional group having a sequence that is complementary to the oligonucleotides bound to the substrate; and

an aggregate probe comprising: (i) at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to  
10 them; (ii) oligonucleotides having bound thereto a specific binding complement of an analyte; and (iii) a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleonucleotide is bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and a second portion of the linker oligonucleotide is bound, as a result of hybridization, to the oligonucleotides  
15 having bound thereto a specific binding complement of an analyte.

559. A kit for detecting a nucleic acid comprising:

a substrate having oligonucleotides attached thereto, the oligonucleotides bound to the substrate have a sequence that is complementary to a first portion of the  
20 nucleic acid;

an oligonucleotide having an sbp member bound thereto, the oligonucleotide having a sequence that is complementary to a second portion of the nucleic acid; and

an aggregate probe for detecting an analyte comprising: (i) at least two  
25 types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them; and (ii) oligonucleotides having bound thereto a specific binding complement of the sbp member, the oligonucleotides having bound

thereto a specific binding complement are bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe.

560. The kit according to claim 559 wherein the sbp member is biotin.

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561. The kit according to claim 559 wherein the specific binding complement of the sbp member is streptavidin or avidin.

562. A kit for detecting a nucleic acid comprising:  
10 a substrate having oligonucleotides attached thereto, the oligonucleotides bound to the substrate have a sequence that is complementary to a first portion of the nucleic acid;

a oligonucleotide having an sbp member bound thereto, the oligonucleotide having the bound sbp member having a sequence that is complementary to a second  
15 portion of the nucleic acid; and

aggregate probes comprising (i) at least two types of nanoparticles having oligonucleotides bound thereto, the nanoparticles of the aggregate probe are bound to each other as a result of the hybridization of some of the oligonucleotides attached to them; (ii) oligonucleotides having bound thereto a specific binding complement of an  
20 analyte; and (iii) a linker oligonucleotide having at least two portions, a first portion of the linker oligonucleotide is bound, as a result of hybridization, to oligonucleotides of at least one of the types of nanoparticles of the aggregate probe; and a second portion of the linker oligonucleotide is bound, as a result of hybridization, to the oligonucleotides having bound thereto a specific binding complement of an sbp member.

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563. The kit according to claim 562 wherein the sbp member is biotin.

564. The kit according to claim 562 wherein the specific binding complement



more biotin molecules, each having an oligonucleotide bound thereto, the oligonucleotide bound to the biotin molecule has a sequence that is complementary to the second portion of the linking oligonucleotide; and

- 5                   contacting the first and second types of nanoparticles, the linking oligonucleotides, and the complex under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles to each other and to the linking oligonucleotide and the hybridization of the oligonucleotides of the complexes to the linking oligonucleotides so that a desired nanomaterials or nanostructure is formed.

- 10               567. A method of nanofabrication comprising:  
                  providing (a) at least one type of linking oligonucleotide having a selected sequence, the sequence of each type of linking oligonucleotide having at least two portions; (b) one or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each type of nanoparticles having a sequence complementary to a  
15               first portion of the sequence of a linking oligonucleotide; (c) biotin having a oligonucleotide bound thereto, the oligonucleotide bound to the biotin has a sequence complementary to a second portion of the sequence of the linking oligonucleotide; and  
                  (d) streptavidin or avidin;

- contacting the linking oligonucleotides, biotin having an oligonucleotide bound  
20               thereto, and nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles and the oligonucleotides bound to the biotin to the linking oligonucleotides to produce a complex; and

- contacting the complex with streptavidin or avidin under conditions effective to allow specific binding interaction between biotin and streptavidin or avidin so that a  
25               desired nanomaterials or nanostructure is formed.

568. A nanomaterial produced by the method comprising:  
                  providing (i) at least one type of linking oligonucleotide having a selected

sequence, the sequence of each type of linking oligonucleotide having at least two portions; (ii) at least two types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on the first type of nanoparticles have a sequence complementary to that of the oligonucleotides on the second type of nanoparticles and a sequence that is complementary to the first portion of the sequence of the linking oligonucleotides, the oligonucleotides on the second type of nanoparticles have a sequence complementary to that of the oligonucleotides on the first type of nanoparticle-oligonucleotide conjugates and a sequence that is complementary to the first portion of the sequence of the linking oligonucleotide; and (iii) a complex comprised of strepavidin or avidin bound to two or more biotin molecules, each having an oligonucleotide bound thereto, the oligonucleotide bound to the biotin molecule has a sequence that is complementary to the second portion of the linking oligonucleotide; and

contacting the first and second types of nanoparticles, the linking oligonucleotides, and the complex under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles to each other and to the linking oligonucleotide and the hybridization of the oligonucleotides of the complexes to the linking oligonucleotides so that a desired nanomaterials or nanostructure is formed.

569. A nanomaterial produced by the method comprising:  
providing (a) at least one type of linking oligonucleotide having a selected sequence, the sequence of each type of linking oligonucleotide having at least two portions; (b) one or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each type of nanoparticles having a sequence complementary to a first portion of the sequence of a linking oligonucleotide; (c) biotin having a oligonucleotide bound thereto, the oligonucleotide bound to the biotin has a sequence complementary to a second portion of the sequence of the linking oligonucleotide; and (d) strepavidin or avidin;

contacting the linking oligonucleotides, biotin having an oligonucleotide bound

thereto, and nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles and the oligonucleotides bound to the biotin to the linking oligonucleotides to produce a complex; and

5 contacting the complex with streptavidin or avidin under conditions effective to allow specific binding interaction between biotin and streptavidin or avidin so that a desired nanomaterials or nanostructure is formed.

570. A method of separating a selected target nucleic acid having at least two portions from other nucleic acids comprising:

10 providing (a) one or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each of the types of nanoparticles having a sequence complementary to the sequence of the first portion of the selected nucleic acid; (b) a complex comprised of streptavidin or avidin bound to two or more biotin molecules, each having a first oligonucleotide bound thereto, the first oligonucleotide having a sequence  
15 complementary to the sequence of the second portion of the selected nucleic acid;

contacting the selected nucleic acid and other nucleic acids with the nanoparticles under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles and the first oligonucleotides of the complex with the selected nucleic acid and subsequent formation of an aggregate; and

20 separating out the aggregate including the selected nucleic acid.

571. A method of separating a selected nucleic acid having at least two portions from other nucleic acids comprising:

25 providing (a) one or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each of the types of nanoparticles having a sequence complementary to the sequence of the first portion of the selected nucleic acid; (b) biotin having an oligonucleotide bound thereto, the oligonucleotide having a sequence complementary to the sequence of the second portion of the selected nucleic acid; and (c)

streptavidin or avidin;

contacting the selected nucleic acid and other nucleic acids with the nanoparticles and biotin having oligonucleotides bound thereto under conditions effective to allow hybridization of the oligonucleotides on the nanoparticles and the oligonucleotides of the biotin construct with the selected nucleic acid and produce a complex;

contacting the complex with streptavidin or avidin under conditions effective to allow specific binding interactions between the biotin and streptavidin or avidin and subsequent formation of an aggregate; and

separating out the aggregate including the selected nucleic acid.

572. A method for accelerating movement of a nanoparticle to an electrode surface comprising the steps of:

providing at least one type of nanoparticle bound to a charged first member of a specific binding pair and an electrode surface including a second member of a specific binding pair;

contacting the nanoparticle and the surface under conditions effective to allow binding between the first and the second members of the specific binding pair; and

subjecting the nanoparticle to an electrical field so as to accelerate movement of the nanoparticle to the surface and facilitate binding between the first and second members of the binding pair.

573. The method of claim 572 wherein the specific binding pair comprises an antibody/antigen.

574. The method of claim 572 wherein the specific binding pair comprises a receptor/ligand.

575. A method of detecting a nucleic acid bound to an electrode surface, the nucleic acid having one or more portions comprising:

providing one or more types of nanoparticles having oligonucleotides attached thereto, the oligonucleotides on each of the types of nanoparticles having a sequence complementary to the sequence of one of the portions of the nucleic acid;





5 582. The method of Claim 577 wherein the detectable change is a color change observable with the naked eye.

583. The method of Claim 582 wherein the color change is observed on a solid surface.

10 584. The method of Claim 577 wherein the nanoparticles are made of gold.

585. The method of Claim 577 wherein the nanoparticles are metallic or semiconductor nanoparticles and the oligonucleotides attached to the nanoparticles are labeled with fluorescent molecules on the ends not attached to the nanoparticles.

15 586. The method according to claim 577 wherein the nucleic acid has at least two portions.

587. The method of Claim 586 wherein:

the nucleic acid has a third portion located between the first and second portions,  
20 and the sequences of the oligonucleotides on the nanoparticles do not include sequences  
complementary to this third portion of the nucleic acid; and  
the nucleic acid is further contacted with a filler oligonucleotide having a sequence  
complementary to this third portion of the nucleic acid, the contacting taking place under  
conditions effective to allow hybridization of the filler oligonucleotide with the nucleic  
25 acid.

588. The method of Claim 577 wherein the nucleic acid is viral RNA or DNA.

589. The method of Claim 577 wherein the nucleic acid is a gene associated with a disease.

590. The method of Claim 577 wherein the nucleic acid is a bacterial DNA.

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591. The method of Claim 577 wherein the nucleic acid is a fungal DNA.

592. The method of Claim 577 wherein the nucleic acid is a synthetic DNA, a synthetic RNA, a structurally modified natural or synthetic RNA, or a structurally modified natural or synthetic DNA.

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593. The method of Claim 577 wherein the nucleic acid is from a biological source.

594. The method of Claim 577 wherein the nucleic acid is a product of a polymerase chain reaction amplification.

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595. The method of Claim 577 wherein the nucleic acid is a fragment obtained by cleavage of DNA with a restriction enzyme.

596. The method of Claim 577 wherein the nucleic acid is contacted with the first and second types of nanoparticles simultaneously.

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597. The method of Claim 577 wherein the nucleic acid is contacted and hybridized with the oligonucleotides on the first type of nanoparticles before being contacted with the second type of nanoparticles.

25

598. The method of Claim 597 wherein the first type of nanoparticles is attached to a substrate.

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599. A method of detecting nucleic acid in a sample, the nucleic acid having at least two portions, said method comprising:

providing a substrate having oligonucleotides attached thereto, the oligonucleotides having a sequence complementary to a first portion of the sequence of a nucleic acid to be detected;

providing a scattered light detectable nanoparticle probe having oligonucleotides attached thereto, the oligonucleotides bound to the nanoparticle probe having a sequence complementary to a second portion of the sequence of said nucleic acid wherein the oligonucleotides are attached to the nanoparticles in a stepwise ageing process comprising (i) contacting the oligonucleotides with the nanoparticles in a first aqueous solution for a period of time sufficient to allow some of the oligonucleotides to bind to the nanoparticles; (ii) adding at least one salt to the aqueous solution to create a second aqueous solution; and (iii) contacting the oligonucleotides and nanoparticles in the second aqueous solution for an additional period of time to enable additional oligonucleotides to bind to the nanoparticles;

contacting said nucleic acid, the substrate and the nanoparticle probe under conditions effective to allow hybridization of said nucleic acid with the oligonucleotides on the nanoparticle probe and with the oligonucleotides on the substrate and form a light scattering complex bound to the substrate;

25 illuminating the light scattering complex under conditions effective to  
produce scattered light from said complex; and

detecting the light scattered by said complex under said conditions as a measure of the presence of the nucleic acid.

600. The method of Claim 599 wherein said nucleic acid is contacted with the substrate so that said nucleic acid hybridizes with the oligonucleotides on the substrate, and said nucleic acid bound to the substrate is then contacted with the scattered light  
5 detectable nanoparticle probe so that said nucleic acid hybridizes with the oligonucleotides on the nanoparticle probe.

601. The method of Claim 599 wherein said nucleic acid is contacted with the nanoparticle probe so that said nucleic acid hybridizes with the oligonucleotides on the  
10 nanoparticle probe, and said nucleic acid bound to the nanoparticle probe is then contacted with the substrate so that said nucleic acid hybridizes with the oligonucleotides on the substrate.

602. The method of Claim 599 wherein said nucleic acid is contacted  
15 simultaneously with the nanoparticle probe and the substrate.

603. The method of Claim 599 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.  
20

604. The method according to Claim 599 wherein said substrate is a waveguide comprising (a) a transparent element having a refractive index greater than that of the fluid sample; (b) a light receiving edge; and (c) a surface having oligonucleotides bound thereto.  
25

605. The method according to claim 604 wherein the illuminating is performed at the light receiving edge of the waveguide with light effective to create total internal reflection within the waveguide, thereby simulataneously illuminating the entire surface

of the waveguide.

606. The method according to claim 603, wherein a plurality of different types of nanoparticles with different sizes or compositions or both are distinguishably detected,  
5 each type of nanoparticles specifically associating with a different nucleic acid sequence.

607. A method of detecting two or more nucleic acids in a sample, each nucleic acid having at least two portions, the method comprising:

providing a substrate having two or more types of oligonucleotides attached  
10 thereto, each type of oligonucleotides attached to a different place on the substrate and each type of oligonucleotides having sequences complementary to a first portion of the sequences of one of nucleic acids to be detected;

providing two or more types of scattered light detectable nanoparticle probes, each type of nanoparticle probes having the oligonucleotides bound thereto, the  
15 oligonucleotides bound to each type of probe have a sequence that are complementary to a second portion of the sequence of one of said nucleic acids to be detected, wherein the oligonucleotides are attached to the nanoparticles in a stepwise ageing process comprising (i) contacting the oligonucleotides with the nanoparticles in a first aqueous solution for a period of time sufficient to allow some of the oligonucleotides to bind to  
20 the nanoparticles; (ii) adding at least one salt to the aqueous solution to create a second aqueous solution; and (iii) contacting the oligonucleotides and nanoparticles in the second aqueous solution for an additional period of time to enable additional oligonucleotides to bind to the nanoparticles;

contacting said nucleic acids, the substrate and the nanoparticle probes under  
25 conditions effective to allow hybridization of said nucleic acids with the oligonucleotides on the nanoparticle probes and with the oligonucleotides on the substrate to form a light scattering complex bound to the substrate;

illuminating the light scattering complex under conditions effective to produce

scattered light from said complex; and

detecting the light scattered by said complex under said conditions as a measure of the presence of one or more nucleic acids.

5           608. The method of Claim 607 wherein said nucleic acids are contacted with the substrate so that said nucleic acids hybridize with the oligonucleotides on the substrate, and said nucleic acids bound to the substrate are then contacted with the scattered light detectable nanoparticle probes so that said nucleic acids selectively hybridize with the oligonucleotides on the nanoparticle probes.

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609. The method of Claim 607 wherein said nucleic acids are contacted with the nanoparticle probes so that said nucleic acids hybridize with the oligonucleotides on the nanoparticle probes, and said nucleic acids bound to the nanoparticle probes are then contacted with the substrate so that said nucleic acids hybridize with the oligonucleotides on the substrate.

15

610. The method of Claim 607 wherein said nucleic acids are contacted simultaneously with the nanoparticle probes and the substrate.

20           611. The method of Claim 607 wherein the substrate has a plurality of types of oligonucleotides attached to it in an array to allow for the detection of multiple portions of a single nucleic acid, the detection of multiple different nucleic acids, or both.

25           612. The method according to Claim 607 wherein said substrate is a waveguide comprising (a) a transparent element having a refractive index greater than that of the fluid sample; (b) a light receiving edge; and (c) a surface having oligonucleotides bound thereto.

613. The method according to claim 612 wherein the illuminating is performed at the light receiving edge of the waveguide with light effective to create total internal reflection within the waveguide, thereby simultaneously illuminating the entire surface of the waveguide.

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614. The method of Claims 599 or 607 wherein the nanoparticles are metal nanoparticles or semiconductor nanoparticles.

615. The method of claim 16 wherein the nanoparticles are gold nanoparticles.

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616. The method of Claims 599 or 607 wherein the oligonucleotides to be bound to the nanoparticles have covalently bound thereto a moiety comprising a functional group that can bind to the nanoparticles.

617. The method of Claims 599 or 607 wherein the moiety comprises a thiol, a polythiol, or a cyclic disulfide group.

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618. The method of Claims 599 or 607 wherein all of the salt is added to the first aqueous solution in a single addition.

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619. The method of Claims 599 or 607 wherein the salt is added gradually over time.

620. The method of Claims 599 or 607 wherein the salt is selected from the group consisting of sodium chloride, magnesium chloride, potassium chloride, ammonium chloride, sodium acetate, ammonium acetate, lithium chloride, tetramethylammonium chloride, a combination of two or more of these salts, one of these salts in a phosphate buffer, and a combination of two or more of these salts in a

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phosphate buffer.

621. The method of claim 619 wherein the salt is sodium chloride in a phosphate buffer.

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622. The method of Claims 599 or 607 wherein the nanoparticles have a diameter ranging between about 10 and about 100 nm.

10 623. The method of Claims 599 or 607 wherein the nanoparticles have a diameter of about 50 nm.

624. The method of Claims 599 or 607 wherein the nanoparticles have a diameter of about 100 nm.

15 625. The method of Claims 599 or 607 wherein two scattered light detectable nanoparticle probes of different diameters are used.

626. The method of claim 624 wherein the nanoparticle probes have a diameter of 50 nm and 100 nm.

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